

NIH Support

for Research on

Women's Health

Issues

Fiscal Vints 1993-1994



Office of Minority Health
Resource Center
PO Box 37337
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for Research on

Women's Health

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Fiscal Years 1993-1994



Office of Research on Women's Health Office of the Director NATIONAL INSTITUTES OF HEALTH

### Preface

This report represents a collaborative effort between the Coordinating Committee on Research on Women's Health (CCRWH); the institutes, centers, and divisions of the National Institutes of Health (NIH); and the Office of Research on Women's Health (ORWH), in conjunction with the Advisory Committee on Research on Women's Health (ACRWH). The CCRWH, as specified by the NIH Revitalization Act of 1993, is composed of the directors (or their designees) of the NIH institutes and is chaired by the director of ORWH; it provides liaison between ORWH and the NIH institutes and centers and promotes collaboration and dialogue between them. This committee, which replaced the former Advisory Committee on Women's Health Issues, assists the ORWH director in identifying the needs for research on women's health, and in encouraging the NIH institutes, centers, and divisions to conduct and support women's health research, including clinical trials. The ACRWH is a panel of non-Federal

physicians, practitioners, scientists, and other health professionals whose clinical practice, research specialization, or professional expertise includes a significant focus on research on women's health. A majority of the members are women. The ACRWH advises the ORWH director on appropriate research activities to be undertaken by NIH regarding research on women's health. The ACRWH provides recommendations on conducting research on women's health conditions and on gender differences in clinical drug trials, and assists in monitoring compliance with the guidelines on inclusion of women in clinical research.<sup>2</sup>

This document is the fourth in a series of NIH reports<sup>3</sup> that highlights research on women's health and provides data on expenditures for research on the health of women and men. The NIH Revitalization Act of 1993 legislatively mandated the establishment of ORWH and specifically required a biennial report describing and evaluating the progress made every 2 years

- (A) advise the Director of the Office on appropriate research activities to be undertaken by the national research institute with respect to
  - (i) research on women's health;
  - (ii) research on gender differences in clinical drug trials, including responses to pharmacological drugs;
  - (iii)research on gender differences in disease etiology, course, and treatment;
  - (iv)research on obstetrical and gynecological health conditions, diseases, and treatments; and
  - (v) research on women's health conditions which require a multidisciplinary approach;
- (B) report to the Director of the Office on such research.

National Institutes of Health Revitalization Act of 1993 (P.L. 103-43), Sec. 486(c): 4) With respect to research on women's health, the Coordinating Committee shall assist the Director of the

Office in-

<sup>(</sup>A) identifying the need for such research, and making an estimate each fiscal year of the funds needed to adequately support the research;

<sup>(</sup>B) identifying needs regarding the coordination of research activities, including intramural and extramural multidisciplinary activities;

<sup>(</sup>C) supporting the development of methodologies to determine the circumstances in which obtaining data specific to women (including data relating to the age of women and the membership of women in ethnic or racial groups) is an appropriate function of clinical trials of treatments and therapies;

<sup>(</sup>D)supporting the development and expansion of clinical trials of treatments and therapies for which obtaining such data has been determined to be an appropriate function; and

<sup>(</sup>E) encouraging the national research institute to conduct and support such research, including such clinical trials."

<sup>&</sup>lt;sup>2</sup>National Institutes of Health Revitalization Act of 1993 (P.L. 103-43), Sec. 486(d): 4) The Advisory Committee shall—

<sup>&</sup>lt;sup>3</sup>Women's Health Research Report: FY 1985-1987; NIH Support for Research on Women's and Men's Health Issues: Fiscal Years 1988-1990; and NIH Support for Research on Women's and Men's Health Issues: Fiscal Years 1991-1992.

in research and treatment of women's health. The NIH Revitalization Act of 1993 defines women's health conditions as follows:

- (1) The term "women's health conditions," with respect to women of all age, ethnic, and racial groups, means all diseases, disorders, and conditions (including with respect to mental health)—
  - (A) unique to, more serious, or more prevalent in women;
  - (B) for which the factors of medical risk or types of medical intervention are different for women, or for which it is unknown whether such factors or types are different for women; or
  - (C) with respect to which there has been insufficient clinical research involving women as subjects or insufficient clinical data on women.
- (2) The term "research on women's health" means research on women's health conditions, including research on preventing such conditions. [Sec. 486(f)]

For presentation in this report, each institute and center submitted to the director of ORWH a report that highlighted, for Fiscal Year 1993 and Fiscal Year 1994, its most significant research programs, summarized its accomplishments in supporting women's health research, listed new initiatives (requests for applications, requests for proposals, program announcements, and workshops and conferences), and identified budget allocations according to gender-specific criteria provided to them.

ORWH greatly appreciates the diligence and dedication of the CCRWH members in contributing to the development of this report. (Please see membership roster on following pages.) We are grateful to the many other staff members of the NIH institutes, centers, and divisions (ICDs) for their efforts in preparing and reviewing the individual reports for the ICDs. We also thank the members of the ACRWH, established in 1994, for their assistance in this undertaking. Finally, we are indebted to the Public Health Service Coordinating Committee on Women's Health and to the staff of the NIH Office of Financial Management for their cooperation and able assistance in the entire process of revising the budgetary reporting categories and in collecting and tabulating budget data

Part I of this report briefly describes the programs and activities of ORWH affecting women's health research and summarizes in tables the research activities funded by ORWH in Fiscal Years 1993 and 1994. Part II, the executive summary, presents (1) the program highlights submitted by each institute and center and (2) a budget analysis that summarizes funding for gender-specific research by health condition. Part III presents the unabbreviated reports from each of the NIH institutes and centers

Vivian W. Pinn, M.D.
Associate Director for Research
on Women's Health
Director of the Office of Research
on Women's Health
National Institutes of Health

# Membership Roster of the Coordinating Committee on Research on Women's Health

Institute, Center or Division	Representative	Title
Division	Representative	THE
WHI	Loretta Finnegan	Co-Director, Women's Health Initiative
NICHD	Judith Whalen	Chief, Office of Science Policy & Analysis
NHLBI	Barbara Packard	Associate Director, Scientific Program Operation
NCRR	Harriet Gordon	Medical Officer, General Clinical Research Centers Program
NIAMS	Lawrence Shulman	Director
FIC	Coralie Farlee	Assistant Director, International Legislation & Activities
NLM	Lois Ann Colaianni	Associate Director, Library Operations
NIGMS	Norka Ruiz Bravo	Genetics Program (Genetics Mechanisms Section)
NIEHS	Anne Sassaman	Director, Division of Extramural Research and Training
NCI	Iris Schneider	Assistant Director, Program Operations & Planning
NIA	Rosemary Yancik	Assistant Director, Liaison & Applied Research
NINR	Sharlene Weiss	Chief, Health Promotion Branch
NINDS	Mary Miers	Chief, Legislation & Analysis Branch
NCHGR	Elke Jordan	Deputy Director
NEI	Richard Mowery	Director, Division of Collaborative Clinical Research
NIDR	Susan Wise	Program Analyst, Planning & Legislation Section
NIDCD	Jay Moskowitz	Deputy Director
NIAID	Holly Taylor	Special Assistant to Director
NIDDK	Nancy Cummings	Associate Director for Research and Assessment
NIMH	Delores Parron	Associate Director for Special Populations
NIAAA	Mary Dufour	Deputy Director, Division of Biometry & Epidemiology
DRG	Donna Dean	Chief, Biological and Physiological Sciences
DCRT	David Rodbard	Director
OD/OEO	Lucretia Coffer	Federal Women's Program Manager
CC	Jean Harris	Nursing Specialist for Quality Assurance
OD	Bonnie Kalberer	Assistant Director, Office of Science Policy & Legislation
OAM	Joseph Jacobs	Director
ORMH	John Ruffin	Director
OAR	Robert Eisinger	Senior Program Analyst

Institute, Center or Division	Alternate	Title
NIDA	Christine Hartel	Acting Director, Division of Basic Research
NICHD	Donna Vogel	Medical Officer, Reproductive Sciences Branch Center for Population Research
NHLBI	Millicent Higgins	Associate Director, Epidemiology & Biometry Program
NCRR	Inese Beitins	Director, General Clinical Research Centers Program
NIAMS	Julia Freeman	Director, Centers Program
FIC	Stephanie Bursenos	Assistant Director for Program Coordination
NLM	Angela Ruffin	Outreach Librarian
NIGMS	Janyce Hedetniemi	Chief, Office of Program Analysis & Evaluation
NIEHS	Terri Damstra	Associate Director, International Programs & Program Coordination
NC1	Cherie Nichols	Chief, Planning & Evaluation Branch
NIA	Shirley Bagley	Assistant Director, Special Programs
NINR	Laura James	Nurse Scientist Administrator
NINDS	Pat Turner	Program Analyst
NCHGR	Jane Peterson	Chief, Mammalian Genomics Branch
NEI	Natalie Kurınij	Health Scientist Administrator
NIDR	Dushanka Kleinman	Deputy Director
NIDCD	Judith Cooper	Deputy Director, Division of Communications Sciences & Disorders
NIAID	Lawrence Prograis	Deputy Director, Division of Allergy, Immunology, & Transplantation
NIDDK	Judith Fradkın	Chief, Endocrinology & Metabolic Diseases Program
NIMH	Deborah Dauphinais	Chief, Women's Mental Health Program
NIAAA	Eleanor Hanna	Special Expert, Division of Biometry and Epidemiology
DRG	Patricia Straat	Deputy Chief for Referral
DCRT	Frances Halverson	Assistant Director
OD/OEO	Dorothy McKelvin	Contract Specialist
CC	Barbara Bowens	Nurse Manager
OD	Anne Houser	Chief, Legislative Liaison and Analysis Branch
OAM		
ORMH		
OAR		

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### Introduction

The research studies described in this report are an integral part of the comprehensive scope of the National Institutes of Health (NIH) intramural and extramural programs that address existing gaps in the scientific knowledge about women's and men's health in the United States. Filling those gaps in scientific knowledge becomes more crucial each year to the Nation's well-being because of the high morbidity and mortality burdens of disease and the spiraling health care cost to the American population. Knowledge is lacking about the causes, expression, and treatment of health conditions among women, in part, because historically women were not frequently included in human subject studies that address lifestyle modifications, risk factor reductions, and intervention strategies for preventing illness and death from acute and chronic diseases. In particular, concerns about women's health issues include the following:1

- Certain health problems are more prevalent in women than in men.
   These problems include cardiovascular diseases, Alzheimer's disease, osteoporosis, immunologic diseases, mental disorders, and disabilities.
- Certain health problems are unique to women or affect women differently than they do men.
   These problems encompass gynecologic

These problems encompass gynecologic malignancies, sexually transmitted diseases, and pregnancy-related problems; they

include lung cancer, cardiovascular diseases, autoimmune diseases, and addictive disorders. Women constitute the population experiencing the most rapid increase in incidence of HIV/AIDS.

#### Overall, women have worse health than men.

Throughout their lives, women have more acute symptoms, chronic conditions, and short- and long-term disabilities arising from health problems. According to the National Center for Health Statistics, in 1990 women contacted their physicians an average of 7 times a year, whereas men contacted their physicians an average of 5.1 times a year.

 More women than men will face the health problems that accompany old age, such as osteoporosis and Alzheimer's disease.

Women constitute the majority of the population. According to the Bureau of the Census, in 1990 women constituted 51.2 percent of the total population. Women historically have had a longer life expectancy than men and make up a majority of the elderly in the United States.

These compelling issues present a formidable challenge to the scientific and health care communities, a challenge to which the NIH institutes and centers are responding collaboratively.

<sup>&</sup>lt;sup>1</sup>Report of the National Institutes of Health: Opportunities for Research on Women's Health, National Institutes of Health, Bethesda, Maryland, NIH Pub. No. 92-3457, September 1992.



### Office of Research on Women's Health

The Office of Research on Women's Health (ORWH) was established by executive action of the Office of the Director of NIH in September 1990 to serve as the focal point for women's health research at NIH, thereby providing leadership in mobilizing the scientific community to provide a better understanding of women's health through biomedical and behavioral research. ORWH was established with the following threefold mandate:

- strengthen and enhance biomedical research related to diseases, disorders, and conditions that affect women and ensure that research conducted and supported by NIH adequately addresses issues regarding women's health through the establishment of a women's health research agenda;
- ensure that women are appropriately represented in biomedical and behavioral research studies supported by NIH; and
- develop opportunities and support for recruitment, retention, reentry, and advancement of women in biomedical careers.

#### ORWH's Expanded Mandate

Subsequently, the NIH Revitalization Act of 1993 provided a legislative mandate for the establishment of ORWH, with directives that intensified ORWH's leadership role in identifying and promoting research of women's health conditions and issues, and requiring that the office address its mandate through the following activities:

- identify projects for research, including multidisciplinary research, that should be conducted on women's health, giving priority to aging in women and menopause;
- promote coordination and collaboration among entities conducting such research;

- recommend an agenda for conducting and supporting such research, and promote the sufficient allocation of resources for such research;
- assist in the administration of mechanisms with respect to the inclusion of women, minorities, and their subpopulations in clinical research funded by NIH, specifically the establishment of guidelines;
- prepare a biennial report on ORWH activities for inclusion in the report that the NIH Director submits to Congress;
- assist the NIH Director, in consultation with the National Library of Medicine (NLM)
   Director, to establish a registry of clinical trials of experimental treatments developed for research on women's health;
- assist the NIH Director, in consultation with the Director of NLM, to establish a data system for the collection, storage, analysis, retrieval, and dissemination of information regarding NIH-funded women's health research;
- assist the NIH Director, in consultation with the NLM Director, to establish, maintain, and operate a program to provide information on NIH research and prevention activities on women's health; and
- assist the Secretary of Health and Human Services (DHHS), acting through the Assistant Secretary for Personnel, to determine the extent to which women are represented among senior physicians and scientists at NIH and among physicians and scientists conducting NIH-supported research, and, as appropriate, to carry out activities to increase such representation.

In the NIH Revitalization Act of 1993, Congress charged NIH to take substantial and specific action in several areas of women's health research. These areas include osteoporosis,

Paget's disease, and related bone disorders; breast, ovarian, and other gynecological cancers; environmental and other risk factors for breast cancer; aging processes; contraception and infertility: DES: obstetrics and gynecology: adolescent health: AIDS: chronic fatigue syndrome; and nutritional disorders. Congress identified specific institutes to carry out its mandates in these areas, thereby providing a number of opportunities for collaboration between ORWH and the NIH institutes and centers on a number of disease-specific research initiatives. Congress also addressed topics of special concern in Senate and House Appropriations Committee Reports in 1993 through 1994. Specifically, topics include those in the Revitalization Act and the following: endometriosis and leiomyomata uteri, menopause, autoimmune disease, systemic lupus erythematosus, urological health, diabetes and coronary artery disease, environmental health, aging among minorities, and cultural/ethnic differences in midlife morbidity.

#### **ORWH Support of Research**

Like other offices within the Office of the Director of NIH, ORWH cannot fund research studies directly, but rather provides funds through NIH institutes and centers. During Fiscal Year 1993, ORWH continued to utilize funding mechanisms to facilitate the implementation of the research agenda developed in 1991 for women's health research and published in the Report of the National Institutes of Health. Opportunities for Research on Women's Health These mechanisms for joint funding allowed ORWH to function as a catalyst and a facilitator, sharing responsibility for women's health research with the multiple institutes and centers of NIH

#### Special Research Initiatives Program

ORWH's special research initiatives program responds to timely opportunities that may arise to support high-quality research that offers the prospect of increasing the knowledge base on women's health, but does not fit within other

FY 1993 ORWH Research Program Summary	Number of	Amount	
Program	Awards	Awarded	
Special Research Initiatives			
Diethylstilbestrol (DES) Research Educational Materials	1	\$ 50,000	
Biology and Pathophysiology of Endometriosis and Leiomyomata Uteri (Myoma)	1	800,000	
Computerization of the Carnegie Collection of Human Embryos	1	10,000	
Evaluation of the Reliability of Newly Developed Research Diagnostic Criteria for Temporomandibular Disorders	1	4,500	
Prevention of Maternal-Fetal Transmission of SIV and HIV	1	16,500	
Intervention Trial of Vaginal Cleansing to Reduce Perinatal Transmission of HIV-1	1	16,500	
Sex Hormone Regulation of Lacrimal Gland Secretion (Dry Eye)	1	81,500	
Multiple Roles of Middle Generation Caregiving Women	1	236,654	
Technology Transfer Conferences: State-of-the-Art			
Diagnosis and Treatment of AIDS in Women	6	250,000	
Subtotal	14	\$ 1,465,654	
Administrative Supplements			
Supplemental Awards (non-AIDS)	73	5,293,947	
AIDS Supplemental Awards	5	496,979	
Subtotal	78	\$ 5,790,926	
Total	92	\$ 7,256,580	

Table 2 FY 1994 ORWH Research Program Summary

Program	Number of Awards	Amount Awarded
Special Research Initiatives		
Multiple Roles of Middle Generation Caregiving Women	1	\$ 132,397
Risk Factors for Physical Disability in Aging Women	1	235,000
Sexual Dimorphism of the Immune System in Sepsis and Traumatic Injury	1	24,876
The Secretary's Conference To Establish a		
National Action Plan on Breast Cancer	1	45,000
Chronic Pain Task Force	1	10,000
Subtotal	5	\$ 447,273
Targeted Research Program		
Autoimmune Diseases		
Chronic Fatigue Syndrome Cooperative Research Center	1	49,902
Silicone Polymers: Tissue and Cellular Response	1	136,679
Program Projects on Autoimmunity	1	300,000
	1	300,000
STDs/Reproductive Health	1	100.000
Adolescent Health Study	1	100,000
Pathophysiology of Endometriosis and	1	654 651
Leiomyomata Uteri		654,651
Menopause and Health in Aging Women	1	573,849
Women's Urological Health		
Collaborative Research Projects on Urinary	1	500,000
Bladder Disorders of Women Subtotal	1 7	500,000 \$ <b>2,315,081</b>
Subtotal	· · · · · · · · · · · · · · · · · · ·	\$ 2,515,001
Administrative Supplements		
Supplemental Awards (non-AIDS)	67	4,630,572
AIDS Supplemental Awards	9	628,299
Subtotal	76	\$ 5,258,871
Total	88	\$ 8,021,225

ORWH programs. These initiatives result either from requests by the NIH institutes and centers for individual projects or from research opportunities identified by the ORWH research agenda in conjunction with the institutes and centers. For special research initiatives, the funding totals were \$1,465,654 in Fiscal Year 1993 (Table 1) and \$447,273 in Fiscal Year 1994 (Table 2) when the targeted research program was initiated.

For example, in Fiscal Year 1993, ORWH co-funded six National Institute of Child Health and Human Development (NICHD) grants for research on the biology and pathophysiology of endometriosis and myoma. A second initiative in reproductive biology is a multi-year project to computerize the Carnegie Collection of Human Embryos into a database of high-resolution digital images of both normal and abnormal embryos during all stages of

development. The database will be available nationwide for genetic and developmental studies to increase scientific understanding of human development and to assist in diagnosis and prevention of birth defects. ORWH. National Cancer Institute, and NICHD collaborated to fund research to enhance early detection of health problems incurred by DESexposed mothers and their offspring and to develop DES educational materials. Other initiatives included research on HIV/AIDS: disorders of lacrimal gland secretion (dry eye), temporomandibular joint disorders; the effects of women's multiple caregiving roles on their mental, social, and physical well-being, and a broad spectrum of basic and clinical women's health research. A special initiative was a joint effort of ORWH and the Office of AIDS Research to develop technology transfer conferences on the diagnosis and treatment of AIDS in women.

In Fiscal Year 1994, through the special initiatives program, ORWH was able to respond to unique and exciting scientific research opportunities. For example, in October 1993, American citizens presented a petition of 2.6 million signatures to U.S. President Bill Clinton, requesting a comprehensive strategy to end the breast cancer epidemic. ORWH assisted DHHS Secretary Donna Shalala in taking a first major step to respond to that request. ORWH and other NIH components developed, convened, and funded the Sccretary's Conference To Establish a National Action Plan on Breast Cancer. Priorities targeting breast health and breast cancer were identified by conference participants, and the conference proceedings provided an action-oriented framework for the pursuit of breast cancer activities in health care, research, and policy. The conference was a collaborative effort involving the National Breast Cancer Coalition, advocacy communities, scientific communities, and numerous components of DHHS and other Federal Government agencies. Following the release of a report from that conference, the lead responsibility for implementing the National Breast Cancer Action Plan was assumed by the Public Health Service Office on Women's Health. Other 1994 initiatives included research on the risk factors for physical disability in aging women and on sexual dimorphism of the immune system in sepsis and traumatic injury.

#### Targeted Research Program

Initiated in Fiscal Year 1994, the targeted research program supports large-scale initiatives with high levels of co-funding for extended periods of time. During Fiscal Year 1994 through NIH mechanisms such as requests lor applications and program announcements, the program emphasized projects that cut across key areas in women's health, have application to NIH-wide programs, and, with sufficient attention and ORWH co-funding have the potential to yield critical data unavailable in the past. In Fiscal Year 1994, the targeted research program identified research in four target areas reproductive health and sexually mune diseases, and occupationally related diseases and disabilities. For targeted research initiatives, the funding total was \$2,315,081 in Fiscal Year 1994

### Administrative Supplements to Ongoing Research Grants

Administrative supplements to ongoing research grants address priority areas either determined annually from among the topics specified in the long-range agenda or identified by the research subcommittee of the Coordinating Committee on Research on Women's Health as topics that require particular emphasis. This program, which supplements ongoing basic and clinical grants with up to \$50,000 per year for 1 to 2 years, emphasized 14 areas of interest in Fiscal Year 1993 and 11 areas in Fiscal Year 1994 (Tables 3–5)

In Fiscal Year 1993, 260 applications were received from the NIH institutes and centers for administrative supplements to ongoing research grants, 78 (30 percent) were funded, including five awards for human immunodeficiency virus (HIV) and AIDS research. The combined value of these awards was \$5,790,926 with an average award of slightly under \$50,000 per study. Basic research accounted for 12 percent of the awards; all other awards supported clinical research. Special consideration was given to projects that would enhance the recruitment of women, particularly minority women, as research subjects and that would demonstrate the feasibility of innovative techniques for recruiting or retaining women as subjects. For example, administrative supplements funded the recruitment of additional postmenopausal women into a study examin-

Table 3
ORWH Administrative Supplements, by Number and IC

FY 1993			FY 1994		
	Number of	Amount	Number of	Amount	
IC	Awards	Awarded	Awards	Awarded	
NCI	9	\$ 657,721	5	\$ 385,190	
NCRR	1	50,000	6	546,610	
NHLBI	5	298,378	5	349,852	
NIAID	4	348,883	1	49,970	
NIAMS	9	531,942	9	739,495	
NICHD	4	300,000	4	296,553	
NIDR			4	342,353	
NIDDK	10	973,224	7	566,271	
NIEHS	1	49,999	2	100,000	
NIGMS	3	200,000			
NIMH	9	643,607	10	485,226	
NINDS	2	145,449			
NINR	7	525,074	1	28,484	
NIA	1	81,074	6	419,316	
NIAAA	7	487,757	6	366,622	
NIDCD	1	50,000	1	49,000	
NIDA	5	447,874	9	533,929	
Total	78	\$ 5,790,926	76	\$5,258,871	

ing endocrine status in response to alcohol among women of different ethnicities and nationalities; an increase in the sample of adolescent girls from rural areas in a study of alcohol use and depression; the addition of Hispanic high school girls to a study of unhealthy weight regulation in adolescent girls; a social marketing strategy for enhancing participation in health promotion programs by hard-to-reach women in manufacturing jobs; recruitment of more minority women into a study of the role of radiolabeled, genetically engineered monoclonal antibodies in the treatment of tumors in colon, rectum, lung, and breast cancer patients; expansion of techniques to retain a cohort of poor, undereducated, minority women in a study of health and depression of young mothers; an increase in the recruitment and retention of minority women in a study of perimenstrual symptoms; the addition of 150 African-American adolescent girls in a study of risk behavior interventions and HIV transmission; and the recruitment

of minority women who have been victims of rape, especially Chicana and Navajo women, into a study of cognitive processing.

In Fiscal Year 1994, 76 (31 percent) of 242 applications for administrative supplements to ongoing research grants were funded for a total of \$5,258,871. Forty-one percent of the awards were in basic research, more than a threefold increase over the previous year. Clinical research accounted for 44 awards. Nine supplements were for HIV/AIDS research (totaling \$628,299).

# Research Planning Conferences and Workshops

Scientific conferences and workshops on biomedical and behavioral research in women's health are valuable mechanisms for assessing the state of the science of a research area, defining important research opportunities that lead to research initiatives, such as requests for applications, or developing action plans for technology transfer. While ORWH cannot provide conference support directly to outside

Table 4
FY 1993 ORWH Administrative Supplements by Disease Category

		0 )	
Subject Area <sup>2</sup>	Title	1C	Amount
Aging	Nursing's Impact on Quality of Life Outcomes in Elders	NINR	\$ 99,822
	Management of Sleep Activity Disruption in Alzheimer's	NINR	49,907
	Alcohol Use and Drug Interactions in Elderly Women	NIAMS	49,472
Alcohol Abuse/	Alcohol Effects in Postmenopausal Women	NIAAA	50,000
Alcoholism	A Prospective Study of Offspring of Alcoholics	NIAAA	37,911
	Naltreone Treatment of Alcohol Dependence	NIAAA	100,000
	Human Alcohol and Aldehyde Dehydrogenases	NIAAA	50,000
	Naltrexone and Cognitive Behavior Therapy of Alcoholism	NIAAA	99,849
	Assessment of Rural Adolescent Alcohol Use	NIAAA	49,997
	Family versus Behavioral Treatment of Alcoholism	NIAAA	100,000
Behavioral	Southeast Asian Women: Their Smoking and Passive Smoking	NHLBI	50,000
Studies	Risk Factors for Unhealthy Weight Regulation	NICHD	100,000
	Caregivers of Alzheimer's Disease Victims: Stress and		
	Mental Health	NIMH	50,000
	Do Food Deprivation and Mood Influence Binge Eating?	NIMH	45,162
	Nursing: Maternal Employment and Low-Birthweight		
	Infant Outcomes	NINR	99,998
	Work Injury and Disability: Gender, Health Care, and Outcome	NIAMS	50,000
Cancer	Progesterone Receptors in Breast Cancer	NCI	100,000
	Growth Control in Aging Fibroblasts	NIA	81,074
	Cervical Dysplasias in Ethnic/Minority Subgroups	NCI	49,893
	Committee on Women's Health—Lung Ancillary	NCI	50,000
	Studies Spermidine N1-acetylase Induction in Lung Cancers	NCI	100,000
	Correlative Studies in Women with Unresectable Meningioma	NCI	100,000
	National Network for Hispanic Cancer Prevention	NCI	74,456
	Accelerating Worksite Smoking Control Programs	NCI	33,382
	Women and Women Minorities in Radioimmunotherapy	NCI	100,000
Cardiovascular	Adaptations to Hypoxia	NHLBI	100,000
Disease	Follow-Up of the 1985-86 NHLBI PTCA Registry	NHLBI	50,000
	Post-Protamine Complement Activation in Cardiac Surgery	NHLBI	48,378
	Follow-Up of the 1985-86 NHLBI PTCA Registry	NHLBI	50,000
	Epidemiology of Lead, Diet, and Blood Pressure	NIEHS	49,999
Depression	Negative Cognition Depression: Etiology and Course	NIMH	100,000
	Mothers—Very Low Birthweight Infants: Anxiety		
	Depression Immune Response	NINR	40,994
	Depressed Children Grown Up: Children at High and		
	Low Risk for Depression	NIMH	99,963
Developmental/	Physiological Factors Affecting Human Lactation	NICHD	50,000
Reproductive Biology	Hormonal Control of the Female Reproductive Tract	NICHD	50,000
- 6/	Nursing Assessment of Premenstrual Syndrome:		
	Neurometric Indices	NINR	84,353
D	Epidemiology of Reproductive Outcome in Lupus	NIAMS	100,000
Digestive Disorders	Psychophysiology of Irritable Bowel Syndrome	NIDDK	100,000
Drug Abuse	Buprenorphine Maintenance for Opioid Addicts	NIDA	99,901
	s listed only once, although many of them could be listed under two or mo		(continued)

Table 4 FY 1993 Administrative Supplements by Disease Category (continued)

Subject Area	Title	IC	Amount
Drug Abuse	Cocaine/Ethylcocaine Metabolism and Behaviors	NIDA	50,000
(continued)	Carbamazepine Treatment in Cocaine Abusers:		
	Victimization in Cocaine-Dependent Women Multi-Ethnic Drug Abuse Prevention Among	NIDA	99,703
	New York Youth	NIDA	99,579
Endocrine Disorders	s Japanese-American Community Diabetes Study	NIDDK	97,867
Genetics	Mouse Mutant Gene Resource	NCRR	50,000
	Ornithine Transcarbamylase Deficiency in Women	NICHD	100,000
	Molecular Basis of Maternally Transmitted Diseases	NIDCD	50,000
	Adrenoleukodystrophy: Studies of Female Heterozygotes	NIDDK	100,000
	Cystic Fibrosis Core Center	NIDDK	98,269
Genitourinary/ Urologic Disease	Host Factors in Susceptibility to Urinary Tract Infection	NIDDK	79,167
Hormonal	Smoking and the Effects of Nicotine in Women	NCI	49.990
Disorders	Disorientation—Model for Nursing Therapy	NINR	50,000
	Porphyrin Biosynthesis in Normal and Disease States	NIDDK	100,000
Immunology	Desensitization of Anti-Idiotypic ABS to MHC Class 1	NIAID	50,000
0,	Mechanisms Mediating Metabolic Changes in Sepsis	NIGMS	50,000
	Immunologic Mechanisms in Lupus Nephritis	NIDDK	100,000
	Autoantibodies to Activated Lymphocytes in Systemic		
	Lupus Erythematosus	NIAMS	50,000
	T-Cell Receptors in Rheumatoid Arthritis	NIAMS	50,000
	Gender Differences in Utilization of Joint Arthroplasty	NIAMS	49,895
	A Prospective Study of Osteoarthritis in Premenopausal Women	NIAMS	43,430
Infectious Diseases	AIDS and Black Women: Testing Risk Behavior Interventions	NINR	100,000
	Anabolic Therapies and Their Metabolic Effects in AIDS	NIDDK	99,405
	Cellular Immunity to HIV in Mothers and Infants	NIAID	98,883
	Adult, AIDS Clinical Trials Unit	NIAID	100,000
	Secondary Prevention with HIV+ Youths in San Francisco, Los Angeles, and New York City	NIDA	98,691
	Vaginotropic and Vaginopathic Strains of Candida Albicans	NIAID	100,000
Namele	New Amino Acid Disorders in Cerebral Disease	NINDS	
Neurology		NINDS	95,715 40,734
01 1	Carbamazepine in Pregnancy		49,734
Obesity	Metabolic Rate and Protein Turnover in Obesity	NIDDK	100,000
_	Food Intake Control by Cholecystokinin in Humans	NIDDK	98,516
Osteoporosis	Skeletal Homeostasis in Blacks and Whites	NIAMS	99,621
	Validation of Biomarkers for Bone Disease in Racially/Ethnically Diverse Populations	NIAMS	39,524
Pharmacokinetics	Pharmacokinetics/Pharmacodynamics	NIGMS	50,000
	Determinants of Individual Responsiveness to Drugs	NIGMS	100,000
Violence	Antisocial and Violent Behavior—Longitudinal Sequelae	NIMH	49,997
	Across Generations: Family Life and Mental Health	NIMH	100,000
	Incest Survivors with Post-Traumatic Stress Disorder:		
	A Comprehensive Treatment	NIMH	48,485
	Mini-Structured Clinical Interview for DSM-III-R		
	Dissociative Disorder	NIMH	50,000
	Cognitive Processing of Traumatic Sexual Victimization	NIMH	100,000

Table 5 FY 1994 ORWH Administrative Supplements by Disease Category

Subject Area <sup>3</sup>	Title	IC	Amount
Aging	Aging of Endocrine Cells in Culture	NIA	\$ 74,000
86	Basic Mechanisms of Aging and Age-Related Diseases	NIA	99,825
	Longitudinal Study—Parents and Children at Age 50	NIA	50,000
	Unique Models for the Study of Menopause	NCRR	100,000
	Reproductive Aging and the Human Hypothalamus	NIA	99,852
	Aromatase in Adipose: Relationship to Aging and Cancer	NIA	50,000
Alcohol Abuse/ Alcoholism	Alcohol Effects in Postmenopausal Women Probabilities of Drunken Driving Among DUIs and	NIAAA	50,000
	U.S. Public Law	NIAAA	67,986
	Psychopharmacologic Treatment of Alcoholism	NIAAA	48,636
	Alcohol, Psychosocial Factors, and Adolescent Development	NIAAA	50,000
Behavioral	Adolescents with Handicaps: Life Span and Cultural Concerns	NICHD	49,885
	Psycholinguistic and Biological Mechanisms in Dyslexia	NICHD	100,000
	Adaptation After Stroke <sup>1</sup> Patient and Support Person Smoking Cessation, Weight Gain, and Exercise in	NINR	28,484
	Underserved Women	NCI	99,287
	Chronically Disabled Adults: Mental Health of Caregivers	NIMH	50,000
	Locomotor Activity Rhythms in Psychiatric Illness	NIMH	50,000
Cancer	Treatment Barriers of Women with Breast Abnormalities	NCI	49,076
	Low-Literacy Informed Consent for Breast Cancer Patients Post-Traumatic Stress Disorder in Life Threatening	NCI	36,869
	Illness—Phenomenology and Risk	NIMH	46,373
	Estrogen and Progesterone Expression in Lung Cancers	NCI	99,958
	Nutritional Biochemistry and Neoplasia in Oral Tissues	NIDR	49,926
	Pheromones, Behavior, and the Regulation of Fertility	NIMH	49,690
	Monkey Models and Women's Health	NCRR	99,999
Cardiovascular	Sex Hormones Modulate Vascular Adrenoceptors in Women	NHLBI	49,921
Disease	Estrogen and Vascular Function in Postmenopausal Women	NHLBI	99,960
	Epidemiology of Lead, Diet, and Blood Pressure	NIEHS	50,000
	Epidemiology of Carotid Artery Disease in Older Adults	NHLBI	50,000
Depression	Behavioral Factors in Coronary Heart Disease	NHLBI	49 971
	Drug Treatment of Depression in Nursing Home Aged	NIMH	49,876
	Relapse and Recurrence in Geriatric Psychotic Depression	NIMH	40,000
Developmental/	Metalloproteinases and Mammary Gland Remodeling	NCI	100,000
Reproductive Biology	Resource Center for Complex Carbohydrates	NCRR	49 997
blology	Bio-Organic Biomedical Mass Spectrometry Resource	NCRR	100,000
	Therapies for Recurrent Miscarriage—A Randomized Study	NICHD	97,012
	Risk Factors Associated with Uterine Fibroid Growth	NICHD	49,656
Drug Abuse	Cocaine/Ethylcocaine Metabolism and Behavioral Studies A High-Risk Prospective Study of Drug Use and Crime:	NIDA	\$ 50,000
	Gender Differences	NIDA	98,061

<sup>&</sup>lt;sup>3</sup>Each supplement is listed only once, although many of them could be listed under two or more of the subject areas.

Table 5 FY 1994 Administrative Supplements by Disease Category (continued)

Subject Area	Title	IC	Amount
Drug Abuse	Drug Effects on Behavior: Workplace Implications	NIDA	49,984
	Evaluating a Desipramine Ceiling in Cocaine Abuse Treatment	NIDA	50,000
	Center For Therapeutic Community Evaluation Research	NIDA	50,000
Endocrine Disorders	Mild Hyperparathyroidism—A Randomized Trial of Surgery Relation of Thyroid Function and Disease to the	NIDDK	87,268
	Menstrual Cycle	NCRR	96,614
Genetics	National Flow Cytometry and Sorting Research Resource National Laboratory	NCRR	100,000
Genitourinary/ Urologic Disease	Epidemiology of Incontinence in African-American Women Recruitment of African-American Females into the African-American Study of Kidney Disease and	NIDDK	49,500
	Hypertension (AASK) Study Enhancing Recruitment of Women in the Full-Scale	NIDDK	81,052
	AASK Trial	NIDDK	48,493
Hormonal Disorders	Hormonal Control of Adipose Gene Expression	NIDDK	100,000
Immunology	T-Cells in the Induction of Lupus	NIAMS	100,000
	Alcohol, Infection, and Host Response	NIAAA	50,000
	Sjögren's Xerostomia: Viral/Immunological Etiology	NIDR	100,000
	Mechanisms and Pathogenesis of Primary Biliary Cirrhosis	NIDDK	100,000
Infectious Diseases	Adolescent Alcohol Use and High-Risk Sexual Behavior	NIAAA	100,000
	Herpes Simplex, Pregnancy, Neonatal Risk, and Host Defense	NIAID	49,970
	Pain in the Ambulatory AIDS Patient CAPS: Adherence to TB and HIV Early Intervention in	NIMH	50,000
	Homeless Adults	NIMH	49,985
	HIV Inhibitory Factors in Human Saliva	NIDR	94,664
	Oral Findings in HIV Infection: Different Risk Groups	NIDR	97,763
	Drugs/AIDS Intervention Among Migrant Workers	NIDA	50,000
	Behavioral Management and Stress Responses in HIV-1	NIMH	49,941
	The Epidemiology of HIV and Health Services Among	NIDA	50,000
	Intravenous Drug Users Each One Teach One—St. Louis' HIV Risk Reduction Study	NIDA	86,070
N. 1	·		
Neurology	Prospective Neuroepidemiology of Adult Lead Exposure Mechanisms of Auditory and Vestibular Dysfunction	NIEHS NIDCD	50,000 49,000
Obesity	Body Fat Distribution and the Metabolic Profile in Women Insulin and Central Nervous System Control of Body	NHLBI	100,000
	Weight and Food Intake	NIDDK	99,958
Osteoporosis	Clinical and Epidemiology Research on Osteoporosis	NIAMS	100,000
	Rickets and Osteomalacia	NIAMS	83,608
	Osteocalcin Synthesis and Catabolism	NIAMS	74,315
	Fractures in Older Women	NIA	45,639
	Multipurpose Arthritis and Musculoskeletal Diseases Center	NIAMS	50,000
	Calcium on Bone Mass Formation During Puberty	NIAMS	100,000
	Effects of Lactation and Weaning on Calcium Status	NIAMS	81,572
	Risk Factors for Vertebral Fracture and Bone Loss	NIAMS	50,000
	Estrogens and Osteoclastogenesis	NIAMS	100,000
Violence	Impact of Family Violence on Women's Drug Use	NIDA	49,814
	Fluoxetine Treatment of Post-Traumatic Stress Disorder	NIMH	49,361

# Table 6 ORWH Co-Sponsored Research Planning Conferences and Workshops, FY 1993-1994

Title	Lead Sponsor
FY 1993	
Aging and Bone Quality Workshop	NIA
Autoimmune Thyroid Disease Workshop	NIDDK
Directions for Menopause Research Workshop	NIA
Extramural Associates Program Update Conference	OD/OER
International Chronic Fatigue Syndrome Myalgie	
Encephomyelitis Research Conference	NIAID
International Conference on Behavioral Research and AIDS	
Prevention in Africa: Meeting the Needs of Women Workshop	NICHD
Older Women, Health, and Retirement: A Demographic Perspective	NIA
Surgeon General's Hispanic Latino Initiative	DHHS/PHS/OASH
Topical Microbicides Workshop	NIAID
Women's Urological Health Research Symposium Workshop	NIDDK
Total Funding	\$41,000
FY 1994	
African-American Women's Health Care	NHLBI
Breast Cancer Education	NCI
Chronic Fatigue Syndrome	NIAID
Endometriosis: Alternatives to Hysterectomy	NICHD
Environmental Risk Factors for Osteoporosis	NIEHS
Health of Women with Physical Disabilities	NICHD
Hormonal Carcinogenesis and Hormonal Cancers	NCI
Measuring Social Inequalities in Health	NICHD
Planning a National Implant Data System	FDA
Psychological and Behavioral Factors in Women's Health	NIMH
Psychosocial Aspects of Reproductive System Disorders	NIMH
Self-Care in Later Life	NIA
Sexually Transmitted Diseases and Adolescents	NIAID
Sexually Transmitted Diseases and Adverse Pregnancy Outcomes	NIAID
Temporomandibular Disorders	NIDR
Temporomandibular Joint Implants	NIDR
Women's Urological Health Research	NIDDK
Total Funding	\$68,000

entities, the office may provide up to \$5,000 co-funding when such conferences or workshops are also being sponsored by an NIH institute or center. Thus, with a small amount of funding, ORWH is able to increase the focus on women's health research priorities. A list of research planning conferences and workshops and their sponsoring institute or center for Fiscal Years 1993-1994 is provided in Table 6.

#### Inclusion of Women in the NIH Clinical Research Studies

NIH policy has addressed the inclusion of women and minorities as subjects in clinical research since 1986. The policy was strengthened and revitalized in 1990. ORWH, the Office of Research on Minority Health, the Office of Extramural Research and Training, and the Office of Intramural Research augmented and implemented new guidelines on the inclusion of women and minorities as specified in the NIH Revitalization Act of 1993, which gave existing policy the force of law and stipulated additional requirements. The revised NIH guidelines, published in the March 28, 1994, Federal Register, were expanded to require that NIH:

- ensure that women and minorities and their subpopulations be included in all human subject research;
- include women and minorities and their subpopulations in Phase III clinical trials such that valid analyses of differences in intervention effect can be accomplished;
- ensure that cost will not be an acceptable reason for excluding these groups; and
- initiate programs and support for outreach efforts to recruit and retain these groups as volunteers in clinical studies.

The revised policy became effective for all applications, proposals, and intramural projects submitted on or after June 1, 1994. In order to comply with the provisions of the new policy, investigators must appropriately recruit and retain in studies participants of both genders, as well as members of diverse racial and ethnic groups. In conducting peer review for scientific and technical merit, reviewers must now:

 evaluate the proposed plan for the appropriate representation and inclusion of women and minorities and their subpopulations;

- evaluate the proposed justification when representation is limited or absent;
- determine whether the design of a clinical trial is adequate to provide valid analysis of any differences between groups; and
- evaluate the plans for recruitment, retention, and outreach for study participants.

The guidelines emphasize that the policy is intended to address gaps in scientific knowledge. A clinical study without appropriate numbers of women or minority subjects may be scientifically flawed, as would be a study without an appropriate control group or one with serious methodological weaknesses. Thus, inclusion should be considered an issue of scientific merit. For this reason, it is the responsibility of peer reviewers to assess a project's inclusion plan as part of their evaluation of the research design. Under NIH review procedures, any application or proposal that is deemed unacceptable with regard to inclusion during initial review receives an administrative bar that precludes the funding of a research award ("bar-to-funding"), as does one found to be unacceptable with regard to the safeguarding of human subjects or the use of vertebrate laboratory animals. When this happens, the situation that caused the bar must be corrected before an NIH research institute or center may lift the bar and make an award.

As part of its approach to integrate the revised guidelines into a biomedical and behavioral research infrastructure, NIH developed and published (August 1994) the Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research, a primer outlining key issues in the recruitment and retention of individuals into studies. To facilitate the appropriate inclusion of study participants, the notebook provides guidance to investigators and their research teams as they consider scientific question(s), study design, and methods.

Dissemination of the guidelines and note-book was largely accomplished through an extensive training program conducted for more than 1,000 NIH staff members who have review, program, or grants management responsibilities. In turn, the trained NIH staff communicated the requirements to grant applicants, reviewers, and other members of the research community. Written guidance provided to NIH staff, reviewers, and applicants

outlined in great detail the circumstances under which it may be acceptable to use study populations that do not have sufficient numbers of women or minority participants, provided the justification is compelling and the scientific objectives of the research are not compromised.

The policy and systems now in place to track adherence to the guidelines were developed through a sequence of activities. In 1993, ORWH formed a Planning Task Force on the Recruitment and Retention of Women in Clinical Studies, whose goals were to:

- assess the clinical trials experience of researchers, practitioners, and women participants in the recruitment, retention, adherence, and compliance of women in clinical research:
- identify issues and barriers unique to the recruitment and retention of women of all races involved in different types of studies, with a particular emphasis on clinical trials;
- review models and approaches that enhance the participation of women in clinical research; and
- develop a summary report with recommendations to the Director of NIH for improving access, participation, and retention of women from all racial and ethnic groups and socioeconomic strata in clinical research.

A major move toward achieving these goals was the March 1993 public hearing held by ORWH and its Task Force on the Recruitment and Retention of Women in Clinical Studies. In response to a Federal Register notice dated March 4, 1993, individuals and representatives of organizations presented oral testimony and/ or submitted written testimony. Major issues related to the recruitment and retention of women in clinical studies were identified, and barriers and recommendations were presented for each issue. The recommendations presented at the public hearing were incorporated into the planning for a scientific meeting, Recruitment and Retention of Women in Clinical Studies, held July 12 and 13, 1993, in Bethesda, Maryland. At that meeting, statements and

presentations by individuals and representatives of national organizations, research institutions, community groups, study participants, and investigators made during the scientific meeting clearly supported the view that a much broader inclusion of women in clinical studies is necessary. In the fall of 1994, ORWH published *Recruitment and Retention of Women in Clinical Studies*, <sup>4</sup> a summary and synthesis of results from the public hearing and the scientific meeting. (This report is available from ORWH.)

A variety of other outreach activities were also initiated to explain the revised policy to the scientific research community and to correct common misunderstandings about the new requirements. To better define the ethical and legal issues associated with including women in clinical studies, especially pregnant women and women of childbearing age, ORWH contracted for a report by the Institute of Medicine. The report, released in February 1994, upheld the importance of including women in clinical studies, stating that women and men should have the opportunity to participate equally in the benefits and burdens of research ORWH also convened a meeting of representative chairs of institutional review boards to discuss their role in implementing the revised policy The NIH staff gave presentations on the 1994 guidelines at numerous professional meetings and workshops. To provide more detailed policy guidance and address some of the more commonly asked questions about implementation of the guidelines, NIH published a book entitled, Questions and Answers Concerning the 1994 NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research.

To monitor compliance with the inclusion requirement, a centralized Gender/Minority Tracking System was developed by the Information Systems Branch, Division of Research Grants, and the NIH Office of Extramural Research, in collaboration with ORWH, the Office of Research on Minority Health, and the NIH Office of Intramural Research. The system was designed to incorporate the standardized reporting format already found in the PHS Form 2590 progress reports, and to be compatible with IMPAC, the existing NIH-wide

<sup>\*</sup>Recruitment and Retention of Women in Clinical Studies, Office of Research on Women's Health, National Institutes of Health, Bethesda, Maryland, NIH Pub. No. 95-3756, 1994.

<sup>&</sup>lt;sup>5</sup>Institute of Medicine. Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies National Academy Press: Washington, DC, 1994.

research data management system. A tracking committee of representatives from each institute, center, and division was established under the leadership of ORWH to meet on a regular basis and coordinate data transfer efforts, address procedural issues in implementation, and discuss lessons learned.

#### Women's Health Initiative

The Women's Health Initiative (WHI) is a study of how to prevent the major causes of death and disability in postmenopausal women in the United States. Established by the director of NIH in 1991, the WHI is the largest prevention study of its kind, funded at \$628 million as a 15-year nationwide endeavor to yield scientific information useful to women and health care providers regarding the risks and benefits of preventive health behaviors. The WHI has three major components: a randomized, controlled clinical trial of promising but unproven approaches to prevention; an observational study to identify predictors of disease; and a study of community approaches to developing healthful behaviors. The Director of ORWH serves as Co-Study Director of the WHI. Dr. Loretta Finnegan, appointed Director of the WHI in December 1994, oversees this study. Recruitment for participants in the study has been underway since 1993 and will continue through January 1998.

The randomized controlled clinical trial component will enroll approximately 64,500 postmenopausal women 50 to 79 years of age. Women may enroll in one or more of the trial's three intervention components. The dietary modifications component will evaluate the effect of a low-fat dietary pattern on prevention of breast and colon cancer and coronary heart disease. The hormone replacement therapy (HRT) component will examine the effects of HRT on prevention of coronary heart disease and osteoporotic fractures. The calcium/vitamin D component will evaluate the effect of calcium and vitamin D supplementation on prevention of osteoporotic fractures and colon cancer. The trial includes a 4-year recruitment period, 9 years of follow-up, and 2 years of data analysis.

Women who are ineligible or unwilling to participate in the trial will be offered the opportunity to enroll in a concurrent longterm observational study that will delineate new risk factors and biological markers for diseases in women. It is expected that about 100,000 women will join this part of the study. Thus, a total of 164,500 women will be studied over time.

The clinical trial and the observational study are being conducted at 40 clinical centers throughout the United States, with a single coordinating center managing data collection and analysis. Sixteen vanguard clinical centers were funded in 1993, and an additional 24 clinical centers were funded in 1994. The broad geographic distribution of the clinical centers allows for recruitment efforts in medically underserved areas and focuses on minority populations across the United States in order to obtain a cross section of the population. Ten clinical centers will recruit primarily minority populations: African Americans, Hispanics, Asian Americans/Pacific Islanders, and Native Americans.

The community prevention study, a study of strategies to enhance the adoption of healthful behaviors, will receive its funding from NIH in 1995 through the Centers for Disease Control and Prevention grants to their Community Prevention Centers: The purpose of the community prevention study is to evaluate strategies to achieve the adoption of healthful behaviors, including improved diet, nutritional supplementation, smoking cessation, increased physical activity, and early detection for women of diverse races, ethnic groups, and socioeconomic strata.

### Developing Opportunities for Women in Biomedical Careers

To fulfill the third part of its mandate—to develop opportunities and support for recruitment, retention, reentry, and advancement of women in biomedical careers—ORWH has developed and supports a wide range of programs and activities in career development for girls and women. ORWH undertook a process to identify the major barriers that women encounter and, while raising the levels of consciousness and concern in the scientific community, developed innovative and successful ways of overcoming the barriers and create pathways for women to enter and advance in biomedical research careers.

In 1992, ORWH convened a Task Force on the Recruitment, Retention, and Advancement of Women in Biomedical Careers to gather information about the issues relevant to the recruitment, retention, and promotion of women in science. The task force received testimony from organizations presented at a March 1992 public hearing. Recommendations from task force deliberations and the public hearing testimonies became the foundation for planning the June 1992 workshop, Women in Biomedical Careers: Dynamics of Change, Strategies for the 21st Century.

Two major outcomes of the public hearing and the workshop on women in biomedical careers were the identification of the major barriers women encounter in biomedical careers and recommendations on how to overcome these barriers. Nine general issues are common to biomedical professional women regardless of race, ethnicity, culture, or scientific discipline:

- · recruiting women into biomedical sciences;
- visibility of role models and mentors;
- · career paths and rewards;
- · reentry into a biomedical career;
- family responsibilities;
- sexual discrimination and sexual harassment;
- research initiatives in women's health:
- sensitizing men to gender career issues; and
- minorities and racial discrimination.

All of the barriers that apply to women in general were identified as being intensified for minority women. As a means of addressing these barriers, the roles of networking, professional organizations, and government were emphasized.

The report of the workshop serves as the foundation for the ORWH strategy to enhance recruitment and promotion of women in science. Some of the recommendations have been translated into funded programs sponsored by ORWH. As described in the following sections, ORWH continued to develop strategies and programs to move forward in implementing the recommendations made at this workshop.

To seek crucial advice in these efforts, ORWH convened a career development subcommittee of the Coordinating Committee on Research on Women's Health. The subcommittee is composed of CCRWH members and other key NIH senior staff. The subcommittee developed the pilot ORWH program for reentry scientists, the NIH Reentry Scientists Program, a reentry scientists workshop, and reentry program assessment instruments.

#### Reentry Scientists Program

The major ORWH career development program is the Reentry Scientists Program, originally developed in 1992 as a pilot program to encourage fully trained women and men to reenter active research careers after taking time off to attend to family needs. Understanding that research skills may lag during a hiatus, ORWH designed the program so researchers could conduct research and also upgrade their research skills and knowledge upon reentry. Thus, the ORWH Reentry Program includes three necessary components, which together contribute to the process of reestablishing awardees as independent, competitive research scientists. (1) full participation in the research project, (2) an opportunity to update and enhance research skills, and (3) a carefully planned mentoring program developed by mentor and awardee. Under the pilot reentry program, ORWH fully funded administrative supplements to support and mentor 16 reentering scientists.

In Fiscal Year 1994, the ORWH pilot program was converted into a trans-NIH program, which is supported by 17 institutes and centers. A program announcement describing this extramural program was published in the NIH Guide for Contracts and Grants. Under this trans-NIH reentry program, ORWH funded seven scientists within this reporting period, with others under consideration for expansion of this initiative. Efforts to promote this program have been widespread and have generated much interest within the scientific community.

In addition, a cooperative intramural program was developed by ORWH and the NIH Office of Education. The intramural reentry program has two goals:

<sup>&</sup>lt;sup>6</sup> Women in Biomedical Careers: Dynamics of Change. Strategies for the 21st Century. Office of Research on Women's Health, National Institutes of Health, Bethesda, Maryland, NIH Pub. No. 95-3565A.

- to encourage fully trained women and men to reenter active research careers in NIH laboratories after taking time off to attend to family needs; and
- to develop a self-perpetuating core of researchers, professors, and teachers who will serve as role models and mentors in attracting and guiding women and minorities into scientific careers.

ORWH fully supported the placement of three scientists, two in the National Cancer Institute and one in the National Institute of Neurological Disorders and Stroke (NINDS) for 2 years.

At the same time, NINDS developed its own extramural career development award (K–17) for Reentry into the Neurological Sciences (RENS). Through this NINDS K–17 award mechanism, ORWH has co-funded two RENS scientists at 50 percent of the award for 2 years.

#### NIH Research Career Program

The NIH Research Career Program provides support both for new and experienced scientists to pursue additional training, receive additional research experience, or develop and implement creative approaches to disease identification and control. In Fiscal Year 1993, ORWH provided funding with the National Institute of Nursing Research for a K-17 award to a new academic investigator for research on prevention of drug abuse by Hispanic women. In Fiscal Year 1994, under a National Research Service Award (F-31), ORWH provided funding with the National Institute of Mental Health for a predoctoral candidate to receive supervised research training on a project investigating the etiology and intervention of athletic menstrual dysfunction.

In addition to these major programs, ORWH often facilitates interaction among the various interest groups representing women at NIH and has sponsored meetings to address career issues for scientists, staff fellows, and summer interns. Furthermore, ORWH collaborated with the institutes and centers and the NIH Office of Education and the NIH Office of Science Education in developing programs for career enhancement and opportunities.

In conjunction with the NIH Office of Education, ORWH sponsored the high school biomedical research program, the inservice and preservice teacher enhancement program, and the undergraduate summer intern program. High school students were given the opportunity to learn about science from the NIH scientists through lectures in NIH laboratories. Teachers from middle schools and high schools were invited to participate in a 7-week summer program, which included a laboratory course, research experience, and seminar series. These efforts were directed toward women and minorities. With the NIH Office of Science Education, ORWH supported brown bag student lunches and a workshop for undergraduates (Strategies for Success for Future Scientists Workshop) to encourage underrepresented minorities, underserved populations, and women to pursue careers in scientific research fields.

#### NCI Science Enrichment Program

In collaboration with the National Cancer Institute (NCI), ORWH co-sponsored the NCI Science Enrichment Program for science education and training opportunities designed to encourage youth from underrepresented minorities and underserved groups—African Americans, Hispanic Americans, Native Americans, and youths from areas where science education opportunities are generally nonexistent or limited—to pursue careers in scientific research fields.

#### Conclusion

In conclusion, in the 4 short years of its existence to Fiscal Year 1994, ORWH advanced significantly toward its goals of directing attention to women's health issues, generating support for research on women's health, stimulating the growth of opportunities for women in biomedical careers, and involving the scientific community nationally in planning and collaborating on programs and in setting the agenda for research on women's health. Within its first 2 years, in collaboration with the NIH institutes and centers, and with the broader research, academic, advocacy, and health care communities, ORWH formulated and disseminated a broad research agenda for women's health based on life span and multidisciplinary concepts. This collaborative effort also resulted in the development of policy recommendations to facilitate an increase in research on conditions that affect the health of women, including strengthening and revitalizing the requirements for including women in human subject research.



### **Executive Summary**

#### HIGHLIGHTS OF INSTITUTE AND CENTER ACTIVITIES

#### Fogarty International Center

The Fogarty International Center (FIC) serves as the focal point for NIH international activities and supports international cooperation in biomedical science through grants, fellowships, international agreements, and other programs. The center also provides international policy guidance to the NIH Director and is the NIH liaison with the Department of State, foreign governments, the World Health Organization, and other international bodies.

Research on women's health is pursued in each of the FIC programs. These include the AIDS International Training and Research Program (AITRP), the Fogarty International Research Collaboration Award (FIRCA) Program, the Scholars-in-Residence Program, and the Senior International Fellowship Program. These programs enable NIH to benefit from research innovations, access information on special populations and environmental conditions in other parts of the world, and provide a way for scientists to share and exchange concepts, data, and experimental methods.

#### National Cancer Institute

Cancer remains the second leading cause of death among women in the United States. In 1995, approximately 258,000 women are expected to die from cancer, including 161,300 from cancers of the lung, breast, colon/rectum, and reproductive tract (uterus, ovary, and cervix). The National Cancer Institute (NCI) supports a comprehensive and coordinated cancer research program to reduce the burden of cancer through targeted research on women's cancer by applying knowledge gained from basic science and research on other forms of cancer.

Discovery and clinical development of new agents to prevent or treat cancer and of novel approaches, including agents that modulate pivotal molecular pathways, vaccines and other immune-based approaches, and gene therapy are high priorities. Studies of the effectiveness of hormonal approaches for both prevention and treatment are underway. NCI funds

research to improve radiation therapy and surgical procedures, especially those that are less invasive and disfiguring. Education and information dissemination efforts encourage women to use appropriate screening methods, such as mammography and Pap testing, and to adopt healthy behaviors to reduce their risk for cancer. NCI also supports research to develop appropriate psychological and social interventions to enhance the quality of life in women with cancer, including older, minority, and underserved women.

A large research effort is directed at understanding the interactive events that occur as a normal cell evolves into an irreversible malignancy. These events may result from inherited abnormalities or from exposure to biological, chemical, or physical agents. NCI supports studies of the genetic and molecular basis of normal and cancer biology; the consequences of hormonal, environmental, and occupational exposures; and risk factors such as diet and personal history. Knowledge gained serves as a foundation for designing new approaches to cancer prevention, early detection and diagnosis, and therapy.

Although the best way to reduce mortality from women's cancers is to reduce incidence, at the present time the ability to reduce mortality depends heavily on early detection of cancer while the tumor is small and localized. To accomplish this, NCI is applying knowledge about cancer biology to the design of sensitive and specific ways to detect small tumors. For example, the usefulness of biomarkers (molecular or other indicators of cancer cells) is being explored. In addition, novel imaging and other technologies are being developed and refined to detect smaller tumors and reduce or eliminate exposure to ionizing radiation.

#### National Center for Human Genome Research

The Human Genome Project is a historic, international research effort that has the goal of analyzing the structure of human DNA and determining the location and sequence of the

estimated 100,000 human genes that constitute the human blueprint. The project evolved from decades of fundamental science research. It is providing researchers with a host of powerful tools and resources to search rapidly and efficiently for disease genes and solve many difficult mysteries of biology and medicine. The resulting acceleration in the pace of gene discovery has been dramatic, with frequent reports in the press of the identification of genes involved in a number of important diseases. The identification of the genetic basis of a wide array of diseases will profoundly change the practice of medicine. Disease gene identification leads to diagnostic tests for individuals at risk, which can open the door to effective preventive medicine measures, and ultimately to new cures from innovative drug therapy or gene therapy approaches. In many other ways, as well, the Human Genome Project will also provide a powerful stimulus for the biotechnology industry and radically alter the future of biomedical research. NIH and the Department of Energy are the key agencies managing this project in the United States.

The National Center for Human Genome Research (NCHGR) was established in 1989 to lead the NIH effort in the Human Genome Project. The NCHGR Division of Extramural Research funds the project's research in laboratories throughout the country. Research in genetic and physical mapping, DNA sequencing, database development, technology development for genome research, and studies of the ethical, legal, and social implications of genetics research are supported by the extramural arm of NCHGR. In February 1993, NCHGR expanded its role at NIH with the establishment of the Division of Intramural Research, focused on applying genome technologies to finding disease genes and developing DNA-based diagnostics and gene therapies. This new division will serve as a hub for human genetics research at NIH, enhancing the work of investigators in other NIH institutes who are searching for specific genes and studying their function in health and disease.

#### National Center for Research Resources

The National Center for Research Resources (NCRR) develops and supports critical research technologies that underpin health-related research to maintain and improve the health of the Nation. NCRR supports shared

resources, sophisticated instrumentation and technology, animal models for study of human disease, biomedical computing, clinical research, and research infrastructure for under-represented groups.

Through its support of multidisciplinary research, NCRR is uniquely positioned to provide either primary research support or resource support in partnership with other institutes and centers to address emerging clinical and basic research needs for women's health research. The expansion of NCRR's present efforts in new technologies and instrumentation, and development of infrastructure, animal models, and clinical research will foster interdisciplinary collaborations and advance the efforts of NIH to support research on women's health

The recent accomplishments in women's health research that are described below exemplify the breadth of science and technology supported by NCRR to promote understanding of normal and abnormal physiology in women and treatment of diseases, disorders, or conditions that are unique to women or that have a significant impact on them. The topics selected include studies of osteoporosis, rheumatoid arthritis, breast cancer, pregnancy and labor, and perinatal HIV infection

#### National Eye Institute

The National Eye Institute (NEI) was created on August 16, 1968, by Public Law 90-489 to conduct and support research, training, health information dissemination, and other programs regarding blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of blind persons.

The major causes of blindness (glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataract) affect both women and men. However, because women live longer than men do on average, more women than men are affected by these age-related eye diseases in the United States. In addition, there appears to be a small excess risk of cataract and macular degeneration for women over that of men.

Several eye conditions affect women significantly more frequently than men. These conditions are optic neuritis, a demyelinating disease of the optic nerve that may be a precursor of multiple sclerosis; dry eye, a common condition that is associated with decreased tear secretion that in most cases causes mild

discomfort but in more severe cases may result in corneal scarring and blindness; and Sjögren's syndrome, an autoimmune disorder that results in severe ocular surface alterations, including decreased aqueous tear production, squamous metaplasia, goblet cell loss, and lymphocytic infiltration.

### National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood; in the uses of blood and the management of blood resources; and in sleep disorders. The diseases that fall within the NHLBI mandate constitute major health concerns for both women and men in the United States. Heart disease, cerebrovascular disease. and chronic obstructive pulmonary disease are the first, third, and fourth most common causes of death in the United States. Many other conditions of interest to the institute (e.g., hypertension, asthma, sickle cell anemia, cystic fibrosis) exact a large toll in terms of the burden of illness and health care costs.

NHLBI supports a range of both observational and interventional studies to identify and elucidate gender differences in manifestations, diagnosis, prognosis, treatment, and risk factors related to diseases within its purview. In addition, the Institute has a significant portfolio of studies focused entirely on women to improve the understanding of how such factors as age, life stage, race/ethnicity, socioeconomic status, lifestyle, and psychosocial influences affect women in health and illness. Three areas of current emphasis are described below.

Coronary Heart Disease: The Institute recently reported the findings of a major clinical trial that evaluated the efficacy and safety of various combinations of sex hormones in improving cardiovascular disease risk factors in postmenopausal women. New studies have been undertaken to determine the effects of hormone replacement therapy and/or antioxidant vitamins on angiographic evidence of atherosclerosis, and to improve the ability to diagnose chest pain in women.

**Primary Pulmonary Hypertension:** An NHLBI-supported study is examining the pattern of primary pulmonary hypertension (PPH) inheritance in a large number of families

to improve understanding of genetic features of this progressive fatal disease. Results of the study to date reveal that more women than men have the gene for PPH and that women with the gene are more likely than men to develop the disease.

Thrombocytopenia: The Institute supports basic and clinical research with the goal of improving diagnosis, treatment, and prevention of this platelet deficiency disorder. Of particular interest is improved management of pregnant women with low platelet counts to ensure the health of the mother and safe delivery of the baby.

### National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Diseases (NIAID) has expanded its women's health efforts to address the national health challenge of disease prevention for women. NIAID supports more research than ever on women's health issues and has intensified its efforts to recruit women for clinical trials. With other institutes across NIH, NIAID has sponsored conferences and workshops, providing a forum for researchers to discuss their findings and explore ways to apply new information and technologies to advance knowledge and understanding of this field of study.

In 1994, NIAID established the Office of Research on Minority and Women's Health (ORMWH), which assists the Institute in the design and implementation of clinical trials that include minorities and women. It also facilitates collaborations between NIAID and the NIH Office of Research on Women's Health (ORWH) and other institutes on research projects involving women. In addition, ORMWH provides information to female students and researchers concerning NIH funding mechanisms and informs the scientific community and the general public about NIAID research on women's health. ORMWH's Women's Health Program coordinator serves as a representative on the ORWH Coordinating Committee on Research on Women's Health.

NIAID conducts a considerable amount of research on women's health issues because many of the diseases within its purview inordinately affect women. For example, systemic lupus erythematosus occurs nine times more often in women than in men. Other diseases,

such as pelvic inflammatory disease, are unique to women. Certain diseases, such as AIDS, are more common in men than women, but the incidence among women is increasing rapidly. Most important, NIAID has sponsored research on maternal/fetal transmission of disease, on topical microbicides, and on the impact and progression of the AIDS epidemic among women and their children.

Of the five research areas in women's health (epidemiology, pathogenesis, diagnosis, prevention, and treatment), NIAID puts particular emphasis on prevention because an effective preventive therapy can save lives and avert suffering. Preventive therapies also have been shown to be extremely cost-effective.

#### National Institute of Arthritis and Musculoskeletal and Skin Diseases

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports and stimulates research on a broad range of diseases and long-lasting, disabling conditions in the areas of rheumatic diseases, bone and mineral metabolism, orthopaedics, muscle biology, and skin diseases. The Institute supports research projects and programs, research training, and career development; collects data on the incidence and prevalence of diseases that are under study; and disseminates research findings to health professionals and the general public.

Significant gaps in knowledge currently exist regarding both women's health issues and gender differences in diseases that affect each sex. NIAMS supports research in the following diseases that are more prevalent in women: osteoporosis, systemic lupus erythematosus, rheumatoid arthritis, fibromyalgia, scleroderma, and Sjögren's syndrome.

# National Institute of Child Health and Human Development

Since its inception, the mission of the National Institute of Child Health and Human Development (NICHD) has included helping families to have healthy babies at the time they are wanted and attempting to ensure that these babies develop without disease or disability, enabling them to achieve a healthy and productive adulthood. Crucial to this mission is the basic need to expand both biomedical and behavioral knowledge concerning female reproduction, including contraception, pregnancy, and fetal development. To achieve this

mission, NICHD supports a multidisciplinary research effort through a variety of program activities with a gender-specific focus.

NICHD's research in the reproductive sciences, for example, includes studying normal reproductive function as well as diseases. disorders, and conditions that affect women's health. This research helps develop knowledge that can be used to regulate fertility or treat female reproductive impairments, such as infertility. Because improving birth outcomes is one of the Institute's overall goals, maternal health during pregnancy becomes a natural focus of research. NICHD-supported researchers strive to understand prerequisites for optimal growth and development by studying nutritional, neural, and hormonal controls of the reproductive process and the roles of these controls throughout the antenatal period, infancy, childhood, adolescence, and adulthood

An additional area of NICHD research involves developing and evaluating safe and effective contraceptive methods, including female-controlled barrier methods that also may be able to protect against sexually transmitted diseases (STDs), including HIV

Much of NICHD's behavioral research on women's health focuses on identifying social and psychological factors that affect birth planning, as well as those that impact the transmission of HIV and other STDs. Sexual behavior and pregnancy among adolescents is an ongoing research emphasis.

#### National Institute of Dental Research

The National Institute of Dental Research (NIDR) conducts and supports research on diseases and disorders that affect the teeth, mouth, jaws, and face, including systemic diseases with oral complications. NIDR also supports research that targets gender differences and spotlights women's unique oral health needs.

NIDR supports research on the inflammatory process, including studies of Sjögren's syndrome, an autoimmune condition that damages salivary and lacrimal (tear) glands and other mucous membranes of the body. In the mouth, salivary gland dysfunction leads to oral dryness, which results in rampant caries, oral sores, and tooth loss. In addition, NIDR operates a dry mouth clinic for the study of xerostomia (dry mouth), resulting from not only disease but the use of radiation therapy

and various medications. The clinic is staffed by scientists who conduct basic research and treat patients by enrolling them in various experimental drug protocols. Another NIDR inflammatory disease focus is rheumatoid arthritis, which cripples as it inflames the joints of the body, including the temporomandibular (jaw) joint. NIDR also supports research on the inflammatory process at the cellular level.

NIDR's sizable pain research portfolio includes basic neurological, clinical, and behavioral studies of orofacial pain. The NIH Pain Research Clinic, under the directorship of NIDR, brings researchers and dental, medical, and nursing professionals together to study pain and find new ways to assess, diagnose, and manage it. Given its proven leadership in the study of pain, NIDR has been asked by Congress to take the lead in developing a report on the frequency and associated health care costs for seven chronic pain conditions, including temporomandibular disorders and reflex sympathetic dystrophy, two chronic pain conditions reported more frequently in women.

NIDR has long fostered basic and clinical research on bones, teeth, cartilage, and other connective tissues. Of special interest are bone and joint diseases that are more prevalent in women, such as osteoporosis and rheumatoid arthritis. The Institute has moved its intramural basic research program to the clinical arena by establishing an NIDR-led bone clinic in the Clinical Center.

# National Institute of Diabetes and Digestive and Kidney Diseases

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports basic and clinical research on diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Within NIDDK's research mission, diseases and health risks that primarily affect women include adult-onset diabetes; gestational diabetes; obesity (especially in minority populations); the eating disorders anorexia nervosa and bulimia; gastric polyposis; osteoporosis; thyroid diseases, including Graves disease, goiter, and hypothyroidism; hyperparathyroidism; gallstones; primary biliary cirrhosis; interstitial cystitis; urinary tract infections; analgesic cystitis; urinary tract infections; analgesic nephropathy; urinary incontinence;

and lupus nephropathy (the kidney disease of systemic lupus erythematosus).

NIDDK supports research directed to chronic diseases of special relevance to women's health. NIDDK has a firm commitment to increasing understanding of disease processes that pose special problems for women and to developing means to treat such diseases. Research supported by NIDDK that involves both women's and men's health includes nutrition research as it relates to coronary artery disease; hypertension; cancer; and the deficiency anemias, including irondeficiency anemia. NIDDK has been one of five NIH institutes supporting the NHLBIinitiated and recently completed Postmenopausal Estrogen Progestin Investigations (PEPI) study—a blinded, placebocontrolled clinical trial of estrogen/progestin combinations in postmenopausal women.

### National Institute of Environmental Health Sciences

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to reduce the burden of environmentally associated diseases and dysfunctions by defining (1) how environmental exposures affect our health, (2) how individuals differ in their susceptibility to these effects, and (3) how these susceptibilities change over time. A number of diseases that predominate in women appear to have an environmental component, including breast cancer, endometrial cancer, osteoporosis, and autoimmune diseases. NIEHS has a long tradition of supporting research related to women's health, and this past year has brought many significant achievements that will advance our understanding in this area.

BRCA1 Gene: NIEHS scientists, working with researchers in Utah, have successfully isolated the breast cancer susceptibility gene, BRCA1. BRCA1 is thought to account for 5 percent of breast cancer cases overall and 25 percent of early-onset (women under age 30) breast cancer cases.

Estrogen Receptor "Knockout Mouse": The female hormone estrogen controls cell growth and differentiation by binding to important estrogen-receptor proteins. Many environmental compounds bind to these same receptor proteins, potentially acting as "environmental estrogens." These environmental compounds, although weakly estrogenic, may

play a role in a wide range of diseases, including endometriosis, uterine fibroids, and cancers of the breast, uterus, and ovaries. NIEHS scientists, collaborating with researchers at the University of North Carolina at Chapel Hill, have developed a transgenic mouse that can aid in defining the role of environmental estrogens in human diseases and dysfunctions. In this mouse an important estrogen receptor has been "knocked out," thereby allowing investigators to evaluate the mechanism of action of hormonally active xenobiotics.

Systemic Lupus Erythematosus: Women are more likely than men to develop autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus (SLE). Environmental factors are thought to play a role in these diseases. One NIEHS grantee has a model system in which mercury-exposed rats develop autoantibodies to laminin, a basement membrane protein. The antibodies formed prevent implantation in pregnant rats; similar antibodies have been found in monkeys and women who have a lot of fetal wastage. Women with SLE have higher rates of spontaneous abortion, and it is thought that their autoimmunity is a contributing factor. This researcher is trying to establish if the autoantibodies in women with SLE are similar to the autoantibodies to laminin in the mercury-exposed rats and, if so, will examine further the environmental factors contributing to the development of autoimmunity.

#### National Institute of General Medical Sciences

Reduction of morbidity and mortality associated with breast cancer relies on prevention, early diagnosis, and effective treatment of the disease. The use of these approaches requires a basic understanding of the etiology of breast cancer—the predisposing factors, the cellular processes that operate in uncontrolled growth of breast tissue, and the mechanisms that promote tumor cell metastasis. The National Institute of General Medical Sciences (NIGMS) supports a broad array of fundamental research in cellular and molecular biology, biochemistry, pharmacology, molecular biophysics, and genetics that impacts on virtually all areas of breast cancer research. NIGMS also supports interdisciplinary research training at the predoctoral and postdoctoral levels that provides the personnel for biomedical research relevant to studies of breast cancer.

#### National Institute of Mental Health

The National Institute of Mental Health (NIMH) conducts research on the causes, diagnosis, treatment, and prevention of mental disorders Mental illnesses are complex disorders, involving the capacities to think, feel, and act. By necessity, the research focus of NIMH is broad. encompassing exploration of the fundamental biology of the brain and basic processes of behavior as well as the interaction between biology and environment Research supported by NIMH has led to major advances in effective therapies and preventive strategies, as well as important insights into biological and psychological foundations of behavioral disorders that affect developmental processes, health status, and quality of life

Research questions related to the risks for, prevalence, and treatment of mental disorders in women historically have been an important part of the NIMH scientific agenda. Over the past decade, development of a sophisticated epidemiologic database has provided a clearer picture of the extent of the various types of mental illnesses in the U.S. adult population overall (not just those seeking clinical care), and of specific real differences between men and women in the prevalence and expression of these disorders.

Valuable information also has been gained about the roles and interactions of biological and environmental factors in mental illness and health, and about the implications of sexrelated biologic factors in understanding the causes and in developing effective treatments for mental illnesses. These trends, along with a climate of growing recognition of the importance of conducting research and evaluating treatments in women, have primed the mental health field for an era of productive, focused study of women's mental health concerns

Old barriers to needed research are now coming down. Historically, out of concern for women during their childbearing years, they have been excluded from early stages of drug development, and studies of medication effects on women have been curtailed. Other barriers have included the complexity and cost of studying interactions of medications with the menstrual cycle in large numbers of women, and a paucity of data from female animals, given the variability associated with the estrus cycle.

While overall prevalence rates of major mental disorders are equivalent for women

and men, important gender differences are seen in the prevalences of specific disorders. Conditions such as major depression and dysthymia affect approximately twice as many women as men. An estimated 6 percent of U.S. women, in contrast to 3 percent of men, will experience a major depression during their lifetime. At least another 6 percent of women have dysthymia, a less severe but often more chronic form of depression. Schizophrenia, too, appears to be marked by gender differences, but in manifestations and course, not prevalence.

Anxiety, panic, and phobic disorders also predominate in women, affecting some two to three times as many women as men. The eating disorders anorexia nervosa and bulimia nervosa (conditions that may be related to obsessive-compulsive behavior) affect women almost exclusively. Anorexia and bulimia together affect 0.5 to 2 percent of adolescent girls and young women, and the prevalence of both is increasing. These disorders can become life-threatening, even lethal; recovery is slow, and relapse is common.

Mental disorders in women are inextricably linked to their own physical health and to the health and well-being of their families. In fact, because women are often caregivers for their parents and children concurrently, a woman's mental disorders may affect two or three generations. Conversely, the burdens of caregiving often can amplify mental disorders.

#### National Institute of Neurological Disorders and Stroke

The National Institute of Neurological Disorders and Stroke (NINDS) conducts and supports research on the causes, diagnosis, treatment, and prevention of neurological and neuromuscular disorders. Most neurological diseases and disorders affect men and women equally. However, there are several nervous system disorders that are more prevalent in, or are of special interest to, women. Research areas relevant to women's health include multiple sclerosis, pain (especially headache), stroke, and myasthenia gravis. Also of interest are the effect of pregnancy on epilepsy seizure activity and the increased risk for fetal death and abnormalities in mothers taking antiepileptic drugs.

**Multiple Sclerosis**: Multiple sclerosis (MS) is a disease caused by inflammation and scarring of the thick sheath, called myelin, that

encases the nerve fibers, resulting in a slowing of electrical impulses. It is one of the most common neurological disorders of young adults and is two to three times as common in women as in men. There are about 250,000 to 300,000 MS patients in the United States, with an estimated 200 new cases diagnosed each week. The costs of medical care, including patient rehabilitation and loss of productivity, represent an economic burden estimated to be in excess of \$2.5 billion annually. Research findings imply that the immune system plays a strong role in the pathogenesis of MS.

Stroke: Stroke is a major health problem for both men and women. Every day more than 1,200 Americans suffer a stroke. About one-third die and another third face permanent disability. Although women in general have a lower risk of stroke than men, because of their longer life expectancy they are vulnerable to the acute effects of stroke and the long-term problems of permanent disability. Subarachnoid hemorrhage is one type of stroke that is more common in women. In 1993, NINDS initiated a clinical trial to examine estrogen therapy and stroke.

Migraine Headaches: Migraine headaches affect millions of Americans, of whom nearly two-thirds are women. Migraine accounts for an estimated 30 million days of lost productivity at a cost of almost \$12 billion annually. Current research is aimed at discovering the etiology of migraine and fostering new treatments.

#### National Institute of Nursing Research

Science is currently engaged in the search for answers to questions about prevailing health problems and the methods for preventing and controlling them. These answers hold potential for transforming our lives and lifestyles. From biology to behavioral science, nursing science stands at the boundary of innovation.

In 1993, the National Center for Nursing Research was redesignated the National Institute of Nursing Research (NINR) by the National Institutes of Health Revitalization Act. The research supported by NINR primarily addresses questions and hypotheses that arise from the direct clinical care of patients and families by nurses. Nursing research includes studies relevant to the diagnosis and treatment of human responses to actual or potential health problems. As such, nursing research includes both scientific inquiries into funda-

mental biomedical and behavioral processes relevant to nursing and research relating to nursing interventions in patient care.

The perspectives employed in the design and conduct of nursing research are multidisciplinary; the outcomes are either for short-term or eventual improvements in nursing practice to enhance disease prevention and promote recovery and maintenance of health. Nursing research considers biomedical, behavioral, and environmental factors that contribute to the causes, prevalence, amelioration, and remediation of illness and disability. A major thrust is the understanding of the biomedical and behavioral underpinning of problems and issues presented in the clinical practice of nursing.

Fifty-two percent of this country's population are women, yet vast knowledge gaps in women's health remain. Women's medical complaints are more than twice as likely as men's to be dismissed by physicians as psychosomatic. Ninety percent of women with breast cancer are eligible for lumpectomies, yet more than half will undergo mastectomies. These are just a few of the penetrating issues galvanizing the women's health movement. Nursing research is addressing women's health concerns by studying normal symptoms, rethinking present treatments, and developing ways to help women make well-informed choices about their own health.

#### National Institute on Aging

The National Institute on Aging (NIA) conducts research on the physiological and behavioral changes that characterize the transition from pre- to post-menopause and on the diseases and disorders related to aging and decreased functional status. Research emphasis is on cancer, osteoporosis, hip fracture, urinary incontinence, and care-giving issues.

Disability and Disease in Older Women: The Women's Health and Aging Study is a prospective study of a sample of 1,000 older community-dwelling women with moderate to severe disability. Data are being collected on nearly 20 major diseases and conditions to ascertain their presence, severity, and impact on disability.

The NIA Epidemiology, Demography, and Biometry Program and the National Cancer Institute Surveillance Program are conducting two studies that will expand the knowledge base on cancer in older women. Tumors of the breast, ovary, and colon are a special

focus because of their severity, especially for women 65 years and older.

Menopause: The Baltimore Longitudinal Study on Aging (BLSA) involves measurements of bone mineral density at 6-month intervals and body composition and blood hormone levels (sex and growth hormones) at 3-month intervals. Another major study, the BLSA Vascular Initiative, is measuring arterial stiffness and cardiac structure and function to ascertain the cause of the dramatic rise in the incidence of hypertension, heart attacks, and strokes in women after menopause.

The Menopause and Health in Aging Women trial will recruit 4,000 women, at least half of whom will be from African-American, Hispanic, and Asian-American populations. Cooperative agreements were awarded to seven clinical sites in Fiscal Year 1994. Studies will (1) characterize biological and psychosocial antecedents and sequelae of the menopausal transition, (2) examine effects of this transition on subsequent health and risk factors for age-related diseases, and (3) identify factors leading to the high utilization of hysterectomies during perimenopause

Physical Frailty/Osteoporosis: The NIA FICSIT (Frailty and Injuries: Cooperative Studies of Intervention Techniques) program consists of eight clinical studies testing interventions to prevent falls and maintain physical abilities in older persons by improving strength, balance, and endurance. In addition, five clinical trials—STOP-IT (Sites Testing Osteoporosis Prevention Intervention/Treatments)—are exploring mechanisms underlying bone loss and responses of older persons to treatment.

### National Institute on Alcohol Abuse and Alcoholism

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) conducts research to improve the treatment and prevention of alcoholism and alcohol-related problems. Alcohol abuse and alcoholism exact tolls of approximately \$98.6 billion each year—yet only a fraction, \$10.5 billion, is devoted directly to treatment for alcoholism, alcohol abuse, and subsequent medical consequences. The remainder can be attributed to lost productivity, excess illness, and early death. Alcohol claimed more than 108,000 lives in 1989—double the number lost to AIDS—while years of potential life lost to alcohol-related diseases exceeded years lost to heart disease and approached the years lost

to cancer. Our health care system registers the repercussions: 20 to 40 percent of patients in urban hospital beds suffer from the effects of drinking regardless of the conditions that initiated their hospitalizations. Among the estimated 13.8 million people in the United States who are alcohol abusers or alcoholic, nearly 4 million are women. Although studies conducted primarily with men have provided much of our knowledge about alcoholism, recent studies involving more women are revealing that prevalence, age at onset, clinical features, course, and outcome of alcohol problems can differ between the genders.

#### National Institute on Deafness and Other Communication Disorders

The National Institute on Deafness and Other Communication Disorders (NIDCD) conducts and supports research and research training on normal mechanisms as well as on diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. NIDCD also conducts and supports research and research training that are related to disease prevention and health promotion. NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The Institute supports efforts to create devices that substitute for lost and impaired sensory and communication functions.

#### National Institute on Drug Abuse

The National Institute on Drug Abuse (NIDA) supports a broad-based program of epidemiological, preclinical, prevention, and treatment research addressing drug abuse and women, as well as gender differences in drug abuse. The program focuses not only on addiction but also on a variety of problems related to drug abuse, including, but not limited to, unwanted pregnancies, STDs, AIDS, crime, violence, and childhood sexual abuse. Furthermore, research has shown that it is imperative that we consider the prevention and treatment of drug abuse and addiction in women within the added context of cultural and ethnic differences, particularly as they are reflected in male-female relationships. Much of NIDA's research on women and gender differences is centered in three research programs.

AIDS in Drug-Using Women: Drug use plays a major role in the spread of AIDS among women. In 1994, 41 percent of women with

AIDS reported injection drug use, and 38 percent reported heterosexual contact with a partner at risk or known to have HIV/AIDS. Among the latter, 38 percent reported having an injecting drug user (IDU) partner. NIDA has established a major program of basic, clinical, and applied research on HIV/AIDS in women, including studies of pathogenesis, epidemiology and natural history, co-morbid conditions, prevention of high-risk behaviors, maternal-infant transmission, effectiveness of HIV-related therapeutics, and access and adherence to treatment. Development of effective interventions and improved treatment for women are NIDA priorities.

Drug Abuse Treatment for Women and the Developmental Effects of Prenatal Drug Exposure: NIDA supports a broad-based, comprehensive program of basic, clinical, prevention, treatment, and epidemiological research addressing a wide range of prenatal drug-exposure issues, including prevalence of exposure, consequences and mechanisms of drug effects, and treatment of the drugabusing pregnant women. In addition, NIDA has recently launched a major effort to establish effective drug abuse treatment for women independently of their reproductive status.

Epidemiology, Etiology, and Prevention: NIDA supports a major epidemiology, etiology, and prevention program aimed at investigating the nature and extent of drug-using behaviors among females and males of all ages and ethnic backgrounds; gender differences in the pathways and determinants of the initiation, progression, and maintenance of drugusing behaviors; gender differences in the social and biological consequences of drug use and abuse; gender differences in the basic behavioral and neurochemical mechanisms of addictions; and gender differences in effective prevention strategies.

#### Office of AIDS Research

Since 1993, AIDS has become the fourth leading cause of death for women aged 25 to 44 in the United States, according to recent statistics from the Centers for Disease Control and Prevention (CDC). In 1994, there were 14,081 reported cases of women with AIDS, and CDC estimates that this number represents only a fourth of actual cases. The number of women known to be HIV-infected is steadily increasing. Epidemiologists believe that the actual number of HIV-infected women is

greater because many more women either do not yet demonstrate symptoms of infection or are unaware of their infection status. While same-sex contact and needle-sharing once accounted for nearly all HIV infections, now there is an ominous increase in heterosexual transmission. The number of women acquiring HIV through heterosexual contact with infected men has increased dramatically in the United States and now totals more than 36 percent of all cases of women with AIDS.

The escalating prevalence of HIV infection in women is a serious public health issue that demands special attention, because the disease appears to affect women in unique ways. Basic research sponsored by NIH has provided and will continue to provide a better understanding of the origins, pathogenesis, and early diagnosis of HIV infection and HIV-associated opportunistic infections and malignancies in women, as well as a better understanding of factors that contribute to maternal-fetal transmission of HIV. NIH also supports drug and vaccine development and evaluation efforts designed to identify, develop, and evaluate new agents for therapy and prophylaxis.

NIH has mounted a concerted effort to identify and determine how HIV disease in women differs from that in men. To understand, prevent, and treat the disease in women, research has been targeted to address a number of issues regarding the following:

- natural history of HIV infection;
- transmission of HIV to women and maternal-fetal transmission;
- factors that affect disease progression;
- clinical, virological, and immunological markers of disease progression; and
- therapeutic needs of women related to gender-specific, high-risk behaviors and psychosocial stressors.

#### NATIONAL INSTITUTES OF HEALTH RESEARCH BUDGET SUMMARY FOR WOMEN AND MEN

This budget summary presents the amounts of funding NIH invested in research during Fiscal Years 1993 and 1994 specific to women, men, and both. The greater part of the NIH budget is spent on research that benefits men and women alike, especially when the research conducted is a clinical trial or basic research. For example, in Fiscal Years 1991 and 1992, 84 percent and 83 percent of the budgets. respectively, were spent on research that was not gender-specific. The approach to data collection for this report is different from that used in earlier reports. In previous years, the budgetary reporting on women's health expenditures focused on single-gender studies. studies to evaluate gender differences, and studies of diseases, disorders, and conditions that are unique to women Previous reporting also used prevalence data as part of the reporting criteria, and included research on diseases, disorders, and conditions that are not unique to one gender, but for which there is documented evidence of greater prevalence in one gender by a ratio of at least 2:1, or for which a specific gender-related consideration exists. Such an approach may not fully reflect the true scope of women's diseases, disorders. and health conditions as currently understood in an expanded concept of women's health research. Therefore, ORWH is collaborating with other Public Health Service (PHS) agencies to coordinate and standardize the procedures for reporting budgetary expenditures on women's health throughout PHS Such procedures will ensure uniformity and consistency in reporting figures on women's health. and will formalize the data collection role of the budget offices of the respective agencies.

"Women's health conditions," as defined in section 486 (f) of the NIH Revitalization Act of 1993, include all diseases, disorders, and conditions that are—

- (A) unique to, more serious, or more prevalent in women;
- (B) for which the factors of medical risk or types of medical intervention are different for women, or for which it is unknown whether such factors or types are different for women; or

(C) with respect to which there has been insufficient clinical research involving women subjects or insufficient clinical data on women.

Research on women's health conditions includes research on preventing such conditions and applies to women of all age, ethnic, and racial groups.

The budgetary figures presented in this report were provided and submitted by the budget officials at the individual institutes and centers, then were compiled by the Office of Financial Management and submitted to ORWH for inclusion in this report.

For the purposes of this report, budgetary expenditures are categorized as inseparably combined or supporting research on either women's health or men's health. As a step toward establishing a uniform procedure for determining the appropriate categorical allocations, ORWH requested the institutes and centers to apply any of the criteria below:

- 1. For research on diseases, disorders, or conditions that occur primarily in women (such as breast cancer and osteoporosis), the entire amount for programs in these areas should be entered under the column listed "women." This includes clinical, applied, and basic research.
- 2. For research on diseases, disorders, or conditions that occur primarily in men (such as prostate cancer and amyotrophic lateral sclerosis), the entire amount for programs in these areas should be entered under the column listed "men." This includes clinical, applied, and basic research.
- 3. For research on diseases, disorders, or conditions that affect both women and men:
  - a) When it can be readily determined what amount may be allocated to women or to men, those amounts should be entered in the appropriate columns. Examples would include clinical research studies where enrollment data or prevalence data give an accurate picture of the respective benefit of the study for women and men.
  - b) When the amount that may be allocated to men and women cannot be readily

determined, the total amount may be entered in the column listed "both." Examples would include many basic research studies, research that is exploring the role of sex and gender differences, and clinical research on diseases, disorders, and conditions that affect both women and men.

For studies on diseases, disorders, and conditions that are unique to women, budgetary reporting is relatively straightforward. In contrast, for diseases, disorders, and conditions that affect both women and men, the most appropriate way to report expenditures continues to be debated. For example, the proportion of expenditures that should be considered to support research on women's health in clinical studies on lung cancer or heart disease may be determined by the proportion of women enrolled in such studies or by the relative prevalence of a condition in women. In other types of research, such as basic research studies, it may be impossible to determine what proportions of the total expenditure should be reported for women or men. Each institute and center applied the criteria according to its discretion and judgment of applicability of a single criterion or combinations of criteria. Even within an institute or center, the same criterion might have been applied differently within distinct projects. ORWH and its advisory and coordinating committees, being aware of these inconsistencies in the currently evolving method for collecting budget data, will carefully monitor the outcomes and will continue to coordinate with the PHS agencies to develop the best method possible for data collection.

Table 7 lists the overall NIH expenditures in Fiscal Years 1993 and 1994 for specific diseases, disorders, and conditions. The health categories and subcategories in Table 7 were developed to accommodate all agencies in PHS. Certain subcategories are not applicable to the NIH mission; for those subcategories, the table shows a "0" across all columns. In some cases. however, a "0" is shown even when the subcategory is appropriate. This occurs because each budget allocation may be listed only once, even though conceptually it applies to more than one category. For example, expenditures for research on infertility are listed under "female reproductive physiology" and "male reproductive disorders."

Table 7. DHHS–National Institutes of Health Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives\*

	FY 1993 Actual				FY 1994 Actual			
	Women	Men	Both	Total	Women	Men	Both	Total
Cancer								
Breast cancer	\$227,206	\$0	\$0	\$227,206	\$300,830	\$0	\$0	\$300,830
(including mammography & other service)								
Reproductive cancers:								
cervical	42,577 33,910	0	0	42,577 33,910	42,778 35,968	0	0	42,778 35,968
ovarian vaginal, uterine, and other	12,620	0	0	12,620	14,568	0	0	14,568
Lung cancer	. 0	0	105,383	105,383	0	141	119,853	119 994
Colorectal cancer	0	0	76,605	76,605	0	0	86,609	86,609
Prostate cancer	0	61,791	0	61,791	0	68,254	0	68,254
Testicular cancer	0	2,721	0	2,721	0	3,080	0	3,080
Penis & other male genital cancers	0	2,233	0	2,233	0	2,162	0	2,162
Head & neck cancer	0	4,421	27,527	31,948	0	5,144	28,051	33,195
Smokeless tobacco & oral cancer	0	0	4,901	4,901	0	0	4,386	4,386
Other neoplasms	170	11	1,228,477	1,228,658	11,653	0	1,304,140	1,315,793
Subtotal	316,483	71,177	1,442,893	1,830,553	405,797	78,781	1,543,039	2,027,617
Cardiovascular/pulmonary								
Blood diseases	118	46	71,952	72,116	44,307	30,108	236,589	311,00-
Heart disease	36,436	27,700	175,322	239,458	60,357	48,984	284,966	394.30
Stroke	54,351	48,761	320,548	423,660	6,839	4,133	85,285	96,25
Other cardiovascular diseases/disorders	6,085	4,912	10,906	21,903	54,187	45,562	242,000	341,749
Pulmonary diseases	53,976	45,999	263,759	363,734	40,731	31,969	215,349	288,049
Hemophilia	34,623	32,414	166,509	233,546	0	17,005	209	17,21
Other	16,722	14,265	60,151	91,138	14,995	1,997	59,630	76,622
Subtotal	202,311	174,097	1,069,147	1,445,555	221,416	179,758	1,124,028	1,525,202
Reproductive & Maternal/Child/Adoles	cent Health							
Contraception	20,015	3,202	4,815	28,032	18,407	2,912	3,602	24,921
Infertility	0	0	0	0	0	0	0	(
Female reproductive physiology	63,451	0	0	63,451	58,274	0	0	58,27-
Hysterectomy	2,686	0	0	2,686	0	0	0	(
Endometriosis/leiomyomas (fibroids)	716	0	0	716	787	0	0	787
Pregnancy/pregnancy prevention maternal health	77,079	0	0	77,079	78,589	0	283	78,872
Child health	2,500	0	136,669	139,169	998	0	108,838	109,836
Adolescent health	5,739	291	61,976	68,006	5,536	291	41,219	47,046
Diseases related to DES exposure	1,302	0	0	1,302	1,515	0	0	1,515
Male reproductive disorders	0	24,341	0	24,341	0	24,571	0	24.57
Mental retardation	3,005	8,058	44,042	55,105	4,901	9,862	49,409	64,172
Other	4,923	1,118	222,595	228,636	5,328	1,144	236,139	242,611
Subtotal	181,416	37,010	470,097	688,523	174,335	38,780	439,490	652,605

	FY 1993 Actual				FY 1994 Actual			
	Women	Men	Both	Total	Women	Men	Both	Total
Aging								
Menopause	5,005	0	0	5,005	9,491	0	0	9,491
Hormone replacement therapy	8,323	0	0	8,323	9,940	0	0	9,940
Alzheimer's disease	3,799	0	259,802	263,601	8,961	0	266,773	275,734
Malnutrition in the elderly	62	63	417	542	62	63	520	645
Incontinence	5,483	0	1,341	6,824	5,091	0	1,355	6,446
Osteoarthritis	0	0	14,112	14,112	0	0	17,784	17,784
Osteoporosis	74,152	3,479	1,939	79,570	79,368	3,700	116	83,184
Women's Health Initiative	41,559	0	0	41,559	59,121	0	0	59,121
Other	14,581	2,411	208,043	225,035	20,066	2,671	186,613	209,350
Subtotal	152,964	5,953	485,654	644,571	192,100	6,434	473,161	671,695
Metabolism/Endocrinology								
Diabetes	88,796	89,282	24,603	202,681	92,776	92,815	31,736	217,327
Nutrition	2,700	2,304	38,229	43,233	2,449	2,131	106,110	110,690
Obesity	21,169	11,060	5,519	37,748	21,869	11,620	7,031	40,520
Hepatobiliary disease	1,640	0	41,940	43,580	752	0	44,800	45,552
Thyroid disease/conditions	15,439	4,750	268	20,457	16,100	0	214	16,314
Urolithiasis Subtotal	0 129,744	3,747 111,143	0 <b>110,559</b>	3,747 <b>351,446</b>	0 1 <b>33,946</b>	3,900 <b>110,466</b>	0 189,891	3,900 <b>434,303</b>
Substance Abuse								
Etiology (unspecified)	305	0	2,101	2,406	0	0	2,378	2,378
Epidemiology (unspecified)	0	0	0	0	0	0	0	0
Prevention (unspecified)	0	0	0	0	0	0	2,379	2,379
Treatment (unspecified)	0	0	0	0	0	0	0	0
Alcohol	3,379	0	129,923	133,302	16,232	198	127,030	143,460
Illegal drugs	60,700	109,915	232,450	403,065	64,560	115,358	244,586	424,504
Prescription drugs	0	0	0	0	0	0	0	0
Tobacco products	0	0	9,749	9,749	0	0	7,148	7,148
Other substances	0	. 0	0	0	0	0	0	0
Co-occurring substance abuse & mental disorders	327	311	3,814	4,452	0	0	5,363	5,363
Subtotal	64,711	110,226	378,037	552,974	80,792	115,556	388,884	585,232
Behavioral Studies/Programs								
Violence (including domestic, abused women, spousal abuse)	4,082	2,507	7,644	14,233	2,184	2,671	11,154	16,009
Behavioral change/ risk-taking behavior	14,582	897	55,623	71,102	13,603	927	56,699	71,229
Cultural/lifestyle factors	397	73	454	924	397	63	313	773
Women as caregivers	1,884	0	0	1,884	1,249	0	1,575	2,824
Other	687	356	20,147	21,190	281	345	18,992	19,618
Subtotal	21,632	3,833	83,868	109,333	17,714	4,006	88,733	110,453

		FY 199	3 Actual		FY 1994 Actual				
	Women	Men	Both	Total	Women	Men	Both	Total	
Mental Health									
Etiology (unspecified)	0	0	9,976	9,976	0	0	9 928	9,928	
Epidemiology (unspecified)	0	0	0	0	0	0	0	0	
Prevention (unspecified)	0	0	556	556	0	0	613	613	
Treatment (unspecified)	0	0	0	0	0	0	0	0	
Depression/mood disorders	9,221	154	46,375	55,750	5,765	198	56 319	62,282	
Suicide	224	0	5,101	5,325	0	101	4 741	4 842	
Schizophrenia	7,169	2,067	56,818	66,054	7,029	2,029	56,515	65 573	
Anxiety disorders	1,396	0	14,213	15,609	0	0	16 793	16 793	
Eating disorders	3,934	0	252	4,186	3,374	0	598	3,972	
Psychosocial stress	4,086	0	19,947	24,033	0	315	25 125	25,440	
Posttraumatic stress disorder (PTSD)	1,132	246	1,473	2,851	0	266	2 533	2 799	
Other mental disorders (excluding Alzheimer's)	17,497	2,477	210,285	230,259	9 357	1 937	218 367	229,661	
Subtotal	44,659	4,944	364,996	414,599	25,525	4,846	391,532	421,903	
Infectious Diseases									
AIDS/HIV	65,366	36,612	736,096	838,074	71,880	21,015	956 426	1,049,321	
Tuberculosis	1,315	1,129	24,669	27,113	1,265	615	37 030	38,910	
Sexually transmitted diseases (STD)	13,027	1,441	45,052	59,520	18,684	3,014	45 088	66,786	
Topical microbicides	6,735	1,156	1,309	9,200	10,076	0	2 124	12,200	
Toxic shock syndrome	348	0	32	380	353	0	0	353	
Chronic fatigue syndrome	2,125	0	1,716	3,841	2,463	0	1819	4,282	
Tropical diseases	154	133	42,830	43,117	389	435	46,918	47,742	
Urinary tract infections	386	122	1,528	2,036	2,447	55	2 195	4,697	
Others Subtotal	11,929 101,385	10,153 50,746	23,667 876,899	45,749 1,029,030	13,313 120,870	10,848 <b>35</b> ,982	147,206 1,238,806	171 367 1,395,658	
Immune Disorders									
Arthritis	1,912	0	107,227	109,139	19,480	70	111,178	130,728	
Lupus erythematosus	19,533	490	6,166	26,189	22,883	290	5,401	28,574	
Multiple sclerosis	37,588	0	31,369	68,957	40,076	70		76,791	
Myasthenia gravis	2,308	0	1,580	3,888	2,380	0	1,529	3,909	
Scleroderma	2,208	0	1,097	3,305	2,943	0	479	3,422	
Sjögren's syndrome	760	0	0	760	1,863	()	0	1,863	
Takayasus disease	0	0	921	921	0	0	231	231	
Other Subtotal	19,066 8 <b>3,375</b>	2,777 <b>3,2</b> 67	13,943 162,303	35,786 248,945	2,955 92,580	2,627 3,057	175,731 331,194	181,313 426,831	
Neurologic, Muscular, and Bone									
Trauma research	0	0	61,788	61,788	0	0	61,315	61.315	
Muscular dystrophy	0	6,153	1,842	7,995	0	6,442	1,935	8,377	
Chronic pain conditions	0	0	14,208	14,208	0	0,112	26,040	26,040	
Temporomandibular disorders	0	0	0	0	0	0	20,010	20,040	
Fibromyalgia & eosinophilic myalgia	483	0	0	483	1,625	0	0	1,625 (continued	

		FY 199	3 Actual		FY 1994 Actual			
	Women	Men	Both	Total	Women	Men	Both	Total
Neurologic, Muscular, and Bone (contin	ued)							
Migraine	680	0	545	1,225	485	0	477	962
Sleep disorders	346	109	12,513	12,968	294	109	11,577	11,980
Paget's disease	0	0	1,061	1,061	0	0	1,044	1,044
Posttraumatic epilepsy	1,611	0	2,682	4,293	1,666	0	3,216	4,882
Amyotrophic lateral sclerosis	0	197	8,818	9,015	0	169	11,025	11,194
Autism	343	1,373	5,549	7,265	0	920	4,119	5,039
Head injury	0	21,926	10,558	32,484	0	26,173	12,082	38,255
Spinal chord injury	0	12,620	4,666	17,286	0	12,364	4,923	17,287
Other Subtotal	5,527 <b>8,990</b>	4,672 <b>47,050</b>	297,220 <b>421,450</b>	307,419 477,490	4,582 <b>8,652</b>	4,747 <b>50,924</b>	312,654 <b>450,407</b>	321,983 <b>509,98</b> 3
Opthalmic, Otolaryngologic, and Oral F	łealth							
Eye diseases & disorders	5,213	3,358	271,866	280,437	6,911	3,617	283,424	293,952
Ear diseases & disorders	2,966	0	87,929	90,895	4,552	0	134,724	139,276
Caries & peridontal disease	1	0	1,461	1,462	0	0	1,264	1,264
Other Subtotal	6,571 <b>14,75</b> 1	1,782 <b>5,140</b>	136,084 497,340	144,437 <b>517,231</b>	10,340 <b>21,803</b>	2,475 6,092	135,000 <b>554,412</b>	147,815 582,307
Health Effects of the Environment								
Environmental estrogens	2,104	0	0	2,104	2,677	0	0	2,677
Health effects of toxic exposure (excluding cancer)	0	0	37,032	37,032	0	0	48,326	48,326
Toxicological research & testing program	0	0	96,690	96,690	0	0	95,227	95,227
Chemical/biological warfare agents	0	0	0	0	0	0	0	C
Other Subtotal	0 2,104	0 <b>0</b>	31,461 <b>165,183</b>	31,461 <b>167,287</b>	0 2,677	0 <b>0</b>	21,706 <b>165,259</b>	21,706 <b>167,93</b> 6
Cross-Cutting Categories and Special II	nitiatives							
Treatment, prevention, & services	718	926	124,792	126,436	589	760	104,871	106,220
Access to health care & financing	0	0	0	0	0	0	0	0
Education & training for health care providers	0	0	0	0	0	0	0	C
Education & training for consumers	0	0	50	50	22,270	0	0	22,270
Bilingual & cross-cultural approaches	0	0	0	0	0	0	0	0
Disability research & services	1,228	931	7,889	10,048	1,105	732	12,191	14,028
Female genital mutilation	0	0	0	0	0	0	0	C
Homeless women	1,483	0	629	2,112	2,131	97	205	2,433
Health statistics & data collection	0	0	0	0	0	0	271	271
Office of Women's Health	9,425	0	0	9,425	10,204	0	0	10,204
Other cross-cutting	0	0	745,376	745,376	322	0	881,659	881,981
Subtotal	12,854	1,857	878,736	893,447	36,621	1,589	999,197	1,037,407
TOTAL: WOMEN'S AND MEN'S HEALTH \$	1,337,379	\$ 626,443	\$ 7,407,162	\$ 9,370,984	\$ 1,534,828	636,271	8 8,378,033	\$ 10,549,13

<sup>\*</sup>NOTE: These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas.

As shown in Table 8, 78-79 percent of the NIH budget supported research that benefits both women and men. Both the total dollars and the proportion of the research budget expended on women's health increased slightly from 14.2 percent in Fiscal Year 1993 to 15.35

percent in Fiscal Year 1994. The total dollars expended on men's health also increased slightly during this period, but its proportion decreased slightly (from 6.68 percent to 6.45 percent).

Table 8. NIH Research Budget Summary by Gender

(Dollars in thousands)

Women		Me	n	Both	*	Total		
FY	\$	%	\$	%	\$	%	S	%
1993	1,337,379	14.27	626,443	6.68	7,407,162	79.04	9,370,984	100
1994	1,548,685	15.35	650,674	6.45	7,890,845	78.20	10,909,204	100

<sup>\*</sup>Excludes the expenditures in the columns for "women" and "men" Includes research that equally and in separably benefits men and women alike, for example, many basic research studies

# Reports of the Institutes and Centers

#### FOGARTY INTERNATIONAL CENTER

The Fogarty International Center (FIC) serves as the focal point for NIH international activities and supports international cooperation in biomedical science through grants, fellowships, international agreements, and other programs. The Center also provides international policy guidance to the NIH Director and is the NIH liaison with the Department of State, foreign governments, the World Health Organization, and other international bodies.

Research on women's health is pursued in all FIC programs. These include the AIDS International Training and Research Program (AITRP), the Fogarty International Research Collaboration Award (FIRCA) Program, the Scholars-in-Residence Program, and the Senior International Fellowship Program. These programs enable NIH to benefit from research innovations, or special populations and environmental conditions in other parts of the world, and to enable scientists to share and exchange concepts, data, and experimental methods.

#### Accomplishments

#### Cardiovascular Studies

A number of studies related to women's health were undertaken by FIC Senior International Fellows. They include the impact of maternal crack use on children in Jamaica. A particularly noteworthy study examined the effect of hostility and depression on increased risk of heart disease and other illnesses. These studies test the hypothesis, in a large sample of older people, including a large number of women, that high levels of hostility have adverse health consequences, such as cardiovascular disease, and showed that hostility was positively associated with increased risk of myocardial infarction (MI) and death.

A person with high hostility scores had a 53 percent greater chance of MI and a 44 percent greater chance of dying during follow-up than a person with low scores. The risk was the same in men and women. Hostility did not predict the incidence of hypertension; however,

it was correlated with low pulmonary function and with high body mass index and not with other coronary risk factors.

Additional studies were undertaken to assess the correlation of depression with health outcomes. Depressed patients had elevated risk of MI and mortality. The relationship to severity of depression indicated that a person need not have serious or clinical depression to be at increased risk. In women, depression was correlated with low pulmonary function and body mass index and with smoking.

The results of these studies show that hostility and depression significantly influence the development of coronary disease and premature mortality in persons over 50 years of age, independent of established risk factors and health behaviors. The effects are equally large for men and women. Further studies are expected to extend these data to persons up to 80 years of age.

Under the FIRCA Program, created to provide awards to the NIH grantees to facilitate their international collaborative activities, a study was supported to assess the effect of estrogen as a buffer to physiologic response to stress. This clinical research complements ongoing work by a U.S. investigator in an animal model on the effects of sex differences and sex hormones on cardiovascular responses to stress, stress-induced hypertension, and the role of neuropeptide-Y. The overall aim of the project is to determine whether sex differences exist in cardiovascular and sympathetic nervous system responses to stress in normal and hypertensive men and premenopausal women.

In addition, data were collected on ovariectomized women with and without estrogen supplementation subjected to (1) cold stress (hand in cold water) and (2) treadmill exercise. Estrogen attenuated the maximal increase in systolic and diastolic blood pressure in response to both stresses, without altering the heart rate responses. The recovery of blood pressure was also faster in women after estrogen supplementation than in women without supplementation. Greater increases

in vascular peptides (NPY, norepinephrine) in response to stress were also observed in normal men than in the no-estrogen phase in women, further supporting a protective role for estrogen against exaggerated responses to cardiovascular stress

#### Maternal and Pediatric AIDS

Under the AITRP, a principal area of study related to women's health is mother-to-child HIV transmission. A scientist from Malawi at The Johns Hopkins University School of Hygiene and Public Health contributed to a study of the status of vitamin A in pregnant Malawian women, as a risk factor for mother-to-child transmission of HIV. Serum vitamin A, height, weight, CD4 T-cell counts, and duration of breastfeeding were measured in 338 HIV-positive mothers whose infant's HIV serostatus was known.

Mother-to-child transmission of HIV was 21.9 percent among mothers whose infants survived to 12 months of age. Vitamin A concentrations in mothers who transmitted HIV to their infants, on average, were lower than that in mothers who did not transmit HIV to their infants. The mother-to-child transmission rates were highest in those mothers with the lowest vitamin A concentrations. Maternal CD4 counts, CD4 percentage, and CD4/CD8 ratios were also associated with increased mother-to-child transmission of HIV. Maternal age, body mass index, and breastfeeding practices were not significantly associated with higher mother-to-child transmission. This study suggests that maternal vitamin A deficiency contributes to mother-tochild transmission of HIV. Additional studies are planned in Malawi and other countries.

#### **Breast Cancer**

Under the Scholars-in-Residence Program, studies were conducted on the etiology of cancer. The growth of normal cells is maintained by a balance of stimulatory and inhibitory signals. When there is a loss or major diminution of inhibitory signals, cells proliferate abnormally and eventually become malignant. A scholar from Germany has detected and isolated a protein from normal mouse mammary glands (designated mammary-derived growth inhibitor, or MDGI) that signals normal breast cells to cease growth. The scholar is collaborating with scientists at the National Cancer Institute to determine whether MDGI

has a similar inhibitory effect on breast cancer cells in women and consequently has potential as a chemopreventive agent

#### NATIONAL CANCER INSTITUTE

#### Accomplishments

Cancer remains the second leading cause of death among women in the United States In 1995, approximately 258,000 women were expected to die of cancer, including 161,300 from cancers of the lung, breast, colon/rectum, and reproductive tract (uterus, ovary, and cervix).

The National Cancer Institute (NCI) has many approaches and programs to evaluate new prevention and treatment strategies and to bring clinical advances to women with cancer, including the Cancer Centers Program, Clinical Trials Cooperative Groups, Specialized Programs of Research Excellence (SPOREs) for breast cancer, and the Community Clinical Oncology Program All NCI-funded clinical trials must include minority populations and have no specific age limitations unless such criteria are dictated by the research question.

NCI supports several programs specifically for breast cancer in addition to the breast cancer SPOREs. Three Breast Cancer Treatment Groups were funded in 1994 through cooperative agreements that allow for interaction with the private and commercial sectors NCI's objective for the groups is to stimulate collaborations between clinicians and laboratory scientists to develop new breast cancer therapies. Along with the National Institute of Environmental Health Sciences and the National Institute on Aging (NIA), NCI is supporting planning grants for cancer centers to establish an organized, interactive infrastructure for breast cancer research. Funds are also provided to centers with existing programs to focus on breast cancer in older women and/or environmental factors influencing the risk for breast cancer. In response to the NIH Revitalization Act of 1993, NCI established an inter-institute working group to coordinate research in breast and gynecologic cancers. This group now includes representatives from other Federal agencies such as the Food and Drug Administration, Department of Defense, and Environmental Protection Agency. In addition, NCI supports a Cooperative Breast Cancer Tissue Registry and is

initiating the Cooperative Family Registry for Epidemiologic Studies of Breast Cancer to facilitate research on breast cancer and to correlate laboratory data about tumors and normal tissues with clinical outcome.

NCI supports extensive education and information programs about cancer prevention and care for the public, patients and their families, and physicians. The Cancer Information Service (CIS) promotes community outreach activities through a network of regional offices, usually linked to NCI-designated regional cancer centers. Through a toll-free telephone number (1-800-4-CANCER), CIS personnel provide information about state-ofthe-art treatment, treatment and prevention clinical trials, and encourage early detection through screening mammography and Pap testing. NCI also operates the Physicians Data Query (PDQ) database, which contains information for the public and for professionals covering cancer treatment, supportive care, screening and prevention, and investigational drugs; summaries of more than 1,500 active and more than 7,000 closed clinical trials; and directories of physicians, professional societies, and organizations active in cancer treatment or screening. Information from the PDQ database is available through several mechanisms including the CIS, direct on-line service to personal computers, compact disk read-only memory (CD-ROM), fax machines (CancerFax®), and the Internet (CancerNet®).

#### **Breast Cancer**

Breast cancer is the second leading cause of cancer death in women and comprises about 30 percent of all female cancers, with 182,000 new cases and 46,000 deaths from breast cancer estimated for 1995. Breast cancer mortality declined 4.7 percent in all American women between 1989 and 1992, the largest short-term decline in the United States for this disease since 1950. For white women aged 30 to 39, mortality decreased 8.7 percent during this period and decreased 17.8 percent for all ages (30 to 79) between 1987 and 1992. NCI believes several factors are involved in the decline in white women, including improved screening, early detection, and use of adjuvant therapy. Especially for women in their thirties, advances in adjuvant therapy might have played a major role in the decline in mortality. The improvement is significant, but continued research is essential to decrease breast cancer

incidence and mortality in women of all ages and ethnic backgrounds.

Unfortunately, the death rate for black women continues to increase (2.6 percent between 1989 and 1992) for reasons that are not clear. A recent NCI-supported study examined several factors contributing to lower survival among black women who experience a 5-year relative survival of only 62 percent. compared with 79 percent for white women. This is partly because black women are likely to have more advanced disease at the time of diagnosis. This could reflect differences in access to care or beliefs about being screened for breast cancer. However, analyses that did not include women with advanced disease at diagnosis still show that breast cancer survival of black women is poorer than that of white women. One reason may be that black women are more likely than white women to have estrogen-receptor negative tumors, which have a poorer prognosis. Research is underway on whether there are other biological characteristics that account for part of the difference in survival.

NCI is working with Federal agencies, the public, and patient advocacy groups to assess progress against breast cancer and to identify research opportunities. In the fall of 1993, the President's Cancer Panel Special Commission on Breast Cancer, after hearing from more than 190 scientists, advocates, and organization and industry representatives, issued a report recommending new directions and priorities for breast cancer research, services, education. and information. In December 1993, the Secretary of the Department of Health and Human Services convened a meeting of government and private sector representatives and consumer advocates to lay the groundwork for developing a broad-based, coordinated strategy against breast cancer. The resulting National Action Plan for Breast Cancer (NAPBC) encompasses three overarching areas: (1) access and use of breast health services, including information dissemination and education; (2) multidisciplinary basic and clinical breast cancer research; and (3) policy actions needed to facilitate changes in approaches to expanding our knowledge about breast cancer, and making high quality breast care available to all women. NCI is a key partner in this plan to reduce the burden of breast cancer. The President's budget for NCI includes \$10

million for Fiscal Year 1995 and requests \$20 million in Fiscal Year 1996 for implementing the NAPBC in collaboration with the Public Health Service Office on Women's Health.

#### Etiology of Breast Cancer

Studies of genes that promote cancer (oncogenes) or inhibit cancer (tumor suppressor genes) and cell cycle regulators (cyclins) are crucial to understanding the molecular mechanisms responsible for the development and eventual control of cancer. Some insights about the genetics of breast cancer have come from research on other cancers. For example, genetic abnormalities that result in loss of control of normal cellular processes, mutations in tumor suppressor genes, were first described in retinoblastoma, a rare childhood cancer of the eve. Families with the Li-Fraumeni syndrome inherit a predisposition for certain cancers. including breast cancer, caused by alterations of the p53 tumor suppressor gene located on chromosome 17. Recently scientists demonstrated that this gene plays a critical role in repairing mistakes in DNA caused by radiation. Other genes important in DNA repair include MSH-2 and MLH-1. Although mutations in these genes were discovered in hereditary colon cancer, these findings apply to many cancers in women, especially endometrial (uterine) cancer but also ovarian and breast tumors.

For many years, scientists have suspected that there is a hereditary basis for some breast cancers. This theory is supported by the existence of families with more than the expected number of early onset breast cancer cases. Researchers, supported in part by NCI, have recently sequenced BRCA1, a breast cancer susceptibility gene on chromosome 17. A normal BRCA1 gene helps to restrain tumor growth. A mutation in this gene can also greatly increase a woman's risk for ovarian cancer. Men who inherit mutations in BRCA1 appear to have a threefold higher than normal risk of developing prostate cancer. There is also a fourfold increased risk for developing colon cancer in men and women from families with BRCA1 mutations. Another breast cancer susceptibility gene, BRCA2, has been mapped to chromosome 13; mutations in this gene do not increase the risk of ovarian cancer. BRCA1 and BRCA2 together account for 70 to 80 percent of all familial breast cancer (5 to 10 percent of all breast cancer). Studies to learn if women with sporadic breast cancer have an

acquired rather than an inherited mutation in one of these genes are underway. To date, consistent mutations of BRCA1 have not been found in women with sporadic breast cancer. The discovery of the location of these genes and the characterization of their mutations move scientists nearer to understanding the origins of breast cancer and may make it possible to identify a subset of women at high risk of developing familial breast cancer.

NCI-supported researchers found that human breast cancer cells have multiple abnormalities in cyclins, the proteins that enable the cell to proceed through the various phases of cell division. These alterations appear to be limited to tumor cells and are not present in adjacent normal tissues. Changes in cyclins may be useful as biomarkers for early detection of pre-malignant lesions in the breast

#### Tumor Metastasis

What makes tumor cells break free from their site of origin and spread to other areas of the body? Two of the crucial mechanisms, angiogenesis and the disappearance of the normal architecture of the tissue, are being extensively investigated by NCI. The formation and proliferation of new blood vessels, angiogenesis. is critical to the growth and spread of tumors. Cytokines, growth factors produced by the tumor cells or by surrounding tissue, drive this process. NCI-supported researchers showed that the amount of one growth factor is elevated in the urine of many cancer patients and may be used as a biochemical marker for metastatic disease or tumor cells remaining after treatment. Direct measurement of the extent of angiogenesis by quantitating microvessel density may also serve as an indicator of metastasis. Another key mechanism in metastasis is the dissolution of the structure of the tissue combined with increased tumor cell motility. One recently discovered gene. maspin, is responsible for producing an inhibitor for an enzyme that destroys proteins. A normal maspin gene keeps this enzyme from disrupting the relationship between cells and thus keeps tumor cells from becoming invasive. Changes in the activity of the maspin gene may serve as a marker of full-blown, invasive cancer.

#### Risk Factors

Evidence from epidemiologic studies suggests that exposure to some environmental agents may play a role in causing breast cancer. NCl

is investigating possible environmental factors in several large-scale studies, including the congressionally mandated Northeast/Mid-Atlantic study and the Long Island Breast Cancer Study Project (LIBSCP). These studies are being conducted in collaboration with the National Institute of Environmental Health Sciences (NIEHS), the Centers for Disease Control and Prevention, the Environmental Protection Agency (EPA), the Department of Energy, and the Department of Agriculture. The LIBSCP also involves six NCI-funded cancer centers in the New York/Long Island region. Specific environmental factors being studied include pesticides and other organochlorines, air pollution (especially aircraft and auto emissions), contaminated drinking water, electromagnetic fields, and hazardous and municipal waste. Dietary factors and exposures to radiation, estrogens, and occupational agents are also being assessed. Pesticides are stored in fat and are potentially important factors in breast cancer development because they have estrogenic activities that may stimulate growth of abnormal cells. NCI, NIEHS, and EPA support the Agricultural Health Study of more than 100,000 farmers and their families to evaluate cancer and other health risks from agricultural exposures including pesticides. NCI is also supporting studies of pesticide exposure in Alaskan natives and in women in Alabama, Michigan, and California. Because studies to date of the possible association between breast cancer and exposure to pesticides have contradictory results, NCI is continuing investigations in this area.

Scientists have known that hormones play an important role in breast cancer and other breast diseases. However, they have had limited success in linking hormone levels in blood and urine to risk of disease. This may be because breast tissue can convert hormone precursors to active hormones. NCI-supported researchers are evaluating the relationship between hormone levels in serum and breast ductal tissue and fat in women with normal breast tissue as well as women with benign breast disease or breast cancer. Other factors will also be considered, including diet, reproductive history, and physical activity, to determine how these affect endogenous (made by the body) hormone levels. The influence of exposures to exogenous (external) hormones, such as diethylstilbestrol, and estrogen replacement therapy are also being studied.

About 12,000 women who had breast augmentation with silicone implants will be studied over several years to assess whether long-term exposure to materials in the implants is carcinogenic or affects the immune system, and whether implants impede early detection of breast cancer.

Epidemiologic studies indicate that some dietary patterns or constituents may be associated with breast cancer incidence and mortality. As part of the NIH Women's Health Initiative (WHI), NCI supports a feasibility study to test methods to encourage women to adhere to a low-fat diet. One objective of the WHI is to test the ability of dietary modification to reduce the incidence of cancer and cardiovascular disease. NCI supports epidemiologic research on the influence of personal history and lifestyle on risk of breast cancer, including a study in women with breast cancer in Finland. This study is analyzing the role of fats, total calories and supplements, as well as genetic markers for breast cancer and reproductive factors. The relationship of childhood nutrition to breast cancer risk factors, including age at menarche, adult height, weight, and amount of body fat, is being investigated. NCI and the American Association of Retired Persons are prospectively examining the association between diet and major cancers, including those of the breast, large bowel, and prostate in 350,000 men and women ages 50 to 69. Data will be collected on a broad range of key nutrients and foods and on cancer-related factors, such as smoking and reproductive histories, hormone use, physical activity, and family history. NCI also supports research on interventions to achieve and sustain healthy dietary changes in minority and underserved populations.

#### Early Detection and Diagnosis

Detection of premalignant lesions before there are symptoms is the goal of screening. Currently, mammography combined with clinical breast examination is the only screening technology that has been shown to reduce breast cancer mortality in women ages 50 and older. However, mammography is not as effective in younger women who have denser breast tissue. To overcome these limitations, NCI is funding research to develop new ways to detect and diagnose breast cancer.

New technologies being developed and evaluated include digital mammography and magnetic resonance imaging (MRI). Digital

mammography, a computer-based technology. is expected to enhance the quality of breast images and improve a radiologist's ability to identify suspicious areas. It is also possible that digital images can be transmitted from remote locations to a site where they can be evaluated by experts. This technology is currently being tested by the United States Army Medical Research and Development Command in consultation with NCI. MRI and related nonionizing technologies may improve the sensitivity of breast cancer screening without exposing healthy breast tissue to radiation. These include magnetic resonance spectroscopy to detect physiologic differences between tumor cells and normal cells and electronic paramagnetic resonance to distinguish normal from malignant tissue by detecting free radicals. Technologies such as positron emission tomography that result in very low radiation exposure are being evaluated, although they are likely to be more useful in staging diagnosed breast cancers than in screening. Other new techniques, including thermal imaging and ultrasound, are being developed. Laser technology is being applied to screening and shows promise for detecting extremely small lesions in heterogeneous, dense breast tissue.

Accurate diagnosis of detected breast lesions is also a high priority for NCI. Fine-needle aspiration of suspicious breast lesions to find out whether they are malignant is widely used. NCI-supported scientists are evaluating the use of imaging techniques to guide the needle precisely to the suspicious area: stereotactically guided needle biopsy. Because there is more efficient collection of cells using this technology, the woman experiences reduced trauma.

Genetic changes and other characteristics of tumor cells may be used as biomarkers, or indicators, to diagnose cancer or detect tumor cells remaining after treatment. Genetic mutations of p53, the multi-drug-resistant gene (MDR), and HER-2/neu are examples of biomarkers under evaluation. NCI is collaborating with the National Center for Human Genome Research (NCHGR) in intramural and extramural studies of changes in the BRCA1 and BRCA2 breast cancer susceptibility genes that can be used as genetic probes or in molecular diagnosis. In collaboration with NCHGR and other NIH institutes, NCI is supporting research to address the ethical, social, and legal implications of tests for breast cancer susceptibility that may soon be available; and to develop counseling,

prevention, and treatment strategies for women at high risk for breast cancer

#### Prevention

Prevention of breast cancer in women at increased risk is a high priority for NCI. In April 1992, NCI began the Breast Cancer Prevention Trial to study the effectiveness of tamoxifen, a hormonal agent long used to treat breast cancer, in preventing breast cancer. The study will include 16,000 women ages 35 and older who are at increased risk for breast cancer for reasons of personal and family history Because a drug is being given to healthy women during this prevention trial, NCI is carefully monitoring women who are receiving tamoxifen to quickly identify any adverse reactions and to adequately assess the risks and benefits that might occur, and take appropriate action. Results of long-term follow-up studies in women with breast cancer who have received tamoxifen show that tamoxifen can decrease recurrence and mortality from breast cancer and reduce the incidence of contralateral breast cancer. There is also evidence that tamoxifen has a favorable effect on serum cholesterol levels and cardiovascular events. and on osteoporosis. Adverse reactions to tamoxifen are rare, although there is an increased risk for endometrial cancer and possibly for blood clots. Participants in the trials are notified as new information becomes available, and if necessary, informed consent documents are updated and appropriate monitoring done. Other agents in various stages of clinical prevention trial evaluation include retinoids, beta-carotene, vitamin E, aspirin, calcium, piroxicam (an antiprostaglandin), and difluoromethylornithene. Compounds under development include vitamin D analogs and raloxifene (a compound similar to tamoxifen). In addition, Oltipraz®, an antiparasitic drug that aids in detoxifying carcinogens, is being tested in Phase I chemoprevention trials for breast and colon cancers.

#### Psychosocial Research

NCI supports research to enhance the quality of life in women with breast cancer. Interventions for the medical, psychosocial, and disability-related sequelae of breast cancer diagnosis and treatment, especially in younger women and women at increased risk for breast cancer, are being developed. NCI collaborates with the National Institute of Child Health and Human Development, the National Institute

on Aging, the National Institute of Nursing Research, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute of Mental Health in these activities.

#### New Approaches to Therapy

Breast cancer is a biologically diverse disease with different cellular and molecular markers and a variety of responses to treatment. Prognostic indicators such as estrogen receptor status, histologic type, and stage at diagnosis are useful determinants of clinical outcome. and in early stages (I and II) breast cancer may influence the choice of therapeutic approach. Research is underway to define the predictive value of newly identified markers and their role in treatment decisions. These include genes or gene products implicated in breast cancer development. For example, even in Stage I disease, where breast cancer has not spread to the lymph nodes, the absence of the protein NM23 is a sign that a tumor is more likely to recur, and new molecular determinants, such as cyclins, mutations in p53, HER-2/neu, and genes controlling angiogenesis, are being uncovered. NCI-supported scientists showed overexpression of HER-2/neu is a sign of aggressive disease and may help identify patients who would benefit from more intensive treatment.

A complex series of events occur in tumor development and metastasis, and basic research is offering new insights into ways to intervene at various steps in the process. Many new drugs being tested with NCI support have a specific molecular target or mechanism of action.

Abnormal cell proliferation is one of the important steps in tumor development. Paclitaxel (Taxol®) stops completion of the cell division process by preventing formation of fibers crucial to the last step of mitosis. This drug, developed by NCI-supported researchers, is a natural product derived from the bark of the Pacific yew tree. Although paclitaxel was originally in short supply, NCI-funded scientists, in cooperation with the pharmaceutical industry, developed methods to extract it from the needles of ornamental yews, a renewable resource, and are close to being able to synthesize the drug. Paclitaxel, which was approved by the Food and Drug Administration in 1992 for refractory ovarian cancer, is now approved for metastatic breast cancer and is being tested in several other cancers as well. NCI-supported researchers showed that mutations in the ras

oncogene confer an increased capacity for proliferation and enhanced survival of many types of tumor cells, for instance colorectal cancers and cancers of the pancreas, bladder, brain, and lung. Although such mutations are rarely found in breast cancer, overexpression of other signalling molecules such as HER-2/ neu may result in changes in ras function that mimic the effects of mutations. NCI is evaluating experimental approaches to cancer therapy and possibly cancer prevention using such agents as limonene (citrus oil), lovastatin, and perillyl alcohol, which disrupt the action of the protein produced by the mutant ras gene.

Stopping metastasis is very important in treating breast cancer. Studies of growth factors and compounds to inhibit metastasis have potential therapeutic value in breast cancer and many other tumor types. The protein produced by the gene NM23 appears to inhibit metastasis, and low levels or absence of this protein are associated with tumor spread. Bryostatin, a natural product currently under clinical development, may elevate the levels of the protein produced by this gene to keep the tumor from spreading. Carboxyamidotriazole (CAI), a synthetic compound that blocks angiogenesis, is in Phase I clinical trials at NCI. This drug, which has a very low toxicity, blocks the flow of calcium into the cell and disrupts the signal transduction pathways (the ways that the elements within cells communicate with one another).

Programmed cell death, or apoptosis, is an active suicide process that occurs when cells are no longer needed or have become damaged. Interruption of this process contributes to the growth of tumors. Restoring normal pathways for apoptosis is a common feature of many chemotherapeutic agents, even though their molecular targets or mechanism of action may vary. Such agents include CAI, lovastatin, paclitaxel, and perillyl alcohol.

Vaccination is a classic tool for preventing disease. Vaccines against tumor cells may eventually be used to prevent cancer in high-risk individuals, but they already show promise in destroying tumor cells that cannot easily be eliminated by surgery or radiation. NCI supports research to uncover and exploit a number of critical tumor cell components, such as carcinoembryonic antigen and mutated p53, which might be used as targets for a vaccine against the tumor.

Women with advanced breast cancer or who have adverse prognostic indicators, such as overexpression of HER-2/neu, may not benefit from standard doses of chemotherapy. Recent studies suggest that the chance of cure may be increased by a higher dose of chemotherapy, but this may be toxic to the bone marrow, thereby increasing the likelihood of infections. This complication can be reduced by autologous bone marrow transplantation (ABMT). Blue Cross and Blue Shield and other insurance companies are helping to pay for patient care costs in NCI-sponsored randomized clinical trials to determine if high-dose chemotherapy with ABMT increases survival in women with advanced or poor prognosis breast cancer

Because of concerns about the effectiveness of breast-conserving surgery (lumpectomy) for localized breast cancer, NCI reanalyzed data from the National Surgical Adjuvant Breast and Bowel Project and other trials of lumpectomy versus mastectomy. Results showed that, for women whose tumors could be resected, lumpectomy with radiation produces survival equivalent to mastectomy. The General Accounting Office issued a report in November 1994 confirming this finding in clinical practice. Women who have had lumpectomies can be reassured that they made a safe choice.

#### Gynecologic Cancers: Ovarian, Endometrial, and Cervical Cancer

In 1995, approximately 26,600 will be diagnosed with ovarian cancer and 14,500 are expected to die from the disease. For endometrial cancer, 32,800 new cases and 5,900 deaths are estimated. Both of these cancers are most common in older women. In 1993, NCI began the intramural gynecologic oncology program to study the natural biology of gynecologic cancers and to develop new approaches to diagnosis and therapy.

#### Ovarian Cancer

The strongest risk factor for developing ovarian cancer is a family history of the disease. The conclusion of the NCI-sponsored NIH Consensus Development Conference on Ovarian Cancer and of the NCI Workshop on Hereditary Breast, Ovarian, and Colon Cancers with NCHGR, held in April 1994, was that up to 10 percent of all ovarian cancer is inherited. Abnormalities of several genes may result in this tumor including BRCA1 (responsible for the breast-ovarian cancer syndrome), MSH-2 and

MLH-1 (DNA repair genes first described in familial colon cancer), and the gene(s) responsible for the familial site-specific ovarian cancer syndrome. Each of these syndromes is inherited as an autosomal dominant disease. To further dissect the molecular causes of ovarian cancer, the multi-institutional Familial Ovarian Cancer Study Group is conducting clinical, epidemiologic, and genetic linkage studies in women at high risk for developing hereditary ovarian cancer. In addition, the NCI extramural Gynecologic Oncology Group is obtaining detailed family histories from women on ovarian cancer clinical trials

Intramural and extramural NCI scientists continue studies of environmental, hormonal, dietary, and reproductive patterns in ovarian cancer. Recent studies show a protective effect in women who lactated before age 20 and who breast fed their babies for at least 6 months. An epidemiologic study in nurses showed that tubal ligation (and to a lesser extent, simple hysterectomy) decreases the risk. NCI is investigating the mechanisms responsible for these observations. One hypothesis is that these procedures result in lower levels of estrogen and progesterone that lead to decreased ovulation. The study also showed that use of oral contraceptives lowers the risk for ovarian cancer

Early detection of ovarian cancer is associated with improved survival. According to the NCI Surveillance Epidemiology and End Results Program (1973 through 1993), 5-year survival for women with local (Stage I) disease is 90 percent, but the 5-year survival in women with regional or metastatic disease is 41 percent and 21 percent, respectively. However, in many women with ovarian cancer, there are no symptoms or only a vague feeling of discomfort, and current detection methods are not sensitive or specific enough. Unique proteins secreted by specific types of cancer cells can be used for early detection of cancer or for following the course of the disease. Measurements of CA-125, a protein found in the serum that is associated with ovarian cancer, is an effective tool. particularly in detecting recurrent disease. Preliminary evidence suggests that the CA-125 assay might also be a good screening tool. To evaluate the usefulness of screening with transvaginal ultrasound and measurements of CA-125 in lowering mortality from ovarian cancer. NCl supports the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, which began accruing patients for a pilot phase in

1993. A total of 37,000 men and 37,000 women will be screened for 4 years for these cancers, and followed for 10 years. An equal number of men and women who receive routine medical care will serve as controls. Normal and pathologic serum and tissues will be collected to test promising biochemical markers for their predictive value. In addition, the risks associated with dietary, hormonal, occupational, and genetic factors will be assessed.

NCI continues to support research to develop and test new treatment strategies for women with ovarian cancer. Phase II clinical trials of intraperitoneal therapy using cytotoxic drugs such as cisplatin, carboplatin, or paclitaxel in combination with 5-Fluorouracil or biologic response modifiers such as interferon are underway to assess the effectiveness of these drugs as adjuvant therapy or therapy for minimal residual disease. Combinations of paclitaxel with other drugs, with and without the granulocytecolony-stimulating factor to reduce the risk of infection, are being evaluated. In addition, the potential for intensive multimodal therapies such as high-dose chemotherapy with ABMT to cure aggressive ovarian cancer is being studied. The current and possible uses of these aggressive therapies were discussed at the 1994 Consensus Development Conference and NCI's May 1993 Cancer Therapy Evaluation Program meeting on High Dose Chemotherapy in Ovarian Cancer.

Angiogenesis, the development and formation of new blood vessels, is important to tumor survival and spread. One growth factor driving this process is the vascular endothelial growth factor (VEGF). VEGF is present in normal ovarian tissue and is important in repair of tissue injury caused by ovulation. One function of this growth factor is to promote permeability of the blood vessels, a possible cause for fluid collecting in the abdomen of ovarian cancer patients, and for the aggressiveness of this cancer. NCI-supported scientists are exploring the implications for new therapeutic approaches to treating ovarian cancer based on these findings.

#### Endometrial (Uterine) Cancer

Endometrial cancers are rare and easily resected at early stages. However, there are disturbing reports of a very small number of aggressive, fatal endometrial cancers arising as a result of treatment of breast cancer with tamoxifen. NCI-supported scientists are studying genetic alterations in these tumors, in particular lesions

in the DNA repair genes MSH-2 and MLH-1, which may be correlated with outcome. To further clarify the extent of this adverse effect of tamoxifen, 500 to 800 women in the Breast Cancer Prevention Trial will undergo serial endometrial biopsies to detect early malignant changes. Furthermore, the efficacy of transvaginal ultrasound to detect early changes and determine who will benefit from endometrial biopsies is being evaluated. To assess the role of tamoxifen in the etiology of endometrial cancer, NCI is supporting a Phase III trial of tamoxifen with pulse progestin versus tamoxifen alone.

#### Cervical Cancer

The incidence of invasive cervical cancer has decreased in the United States over the past several years. This trend is likely due to early Pap smear detection of cervical intraepithelial neoplasia (CIN) or carcinoma in situ, noninvasive lesions that can be cured. In 1995. 15.800 women are expected to be diagnosed with invasive cervical cancer, and 4,800 are expected to die from the disease. Worldwide 200,000 deaths from cervical cancer are expected, many of which could be prevented by screening. Although many factors have been implicated in cervical cancer carcinogenesis, studies over the last 5 years show that infection with some types of human papilloma virus (HPV) is strongly associated with this cancer. Scientists are now characterizing the molecular changes that accompany these infections and have found that certain growth factors, including the platelet-derived growth factor and the epidermal growth factor, are activated by proteins produced by these virus types. NCI scientists are also exploiting the immunogenicity of HPV-16 as the basis for a screening test that will detect antibodies in serum. Studies are underway in the Prostate, Lung, Colorectal, and Ovarian Trial to correlate the results of this screening with Pap tests and the development of CIN or cervical cancer.

NCI-supported investigators are conducting large population-based studies of women around the world to define the full spectrum of viral (including co-infections with Herpes simplex II and HIV), immunologic, hormonal, and lifestyle factors that contribute to development of cervical cancer. Such studies will identify women who might benefit from prevention trials with drugs such as retinoids and folic acid or with HPV vaccines.

#### Lung Cancer

Lung cancer continues to be the leading cause of cancer deaths in women, with 73,900 new diagnoses expected in 1995 and 62,000 deaths. The majority of these cases are a result of tobacco use. NCI is supporting basic research of the underlying factors associated with lung cancer carcinogenesis. An understanding of these factors will guide prevention and treatment efforts. Many mutations, deletions, or amplifications of growth-promoting oncogenes and growth-inhibiting, tumor-suppressor genes have been found in lung cancer, including mutations of p53, the retinoic acid receptorbeta (RAR) gene, and the raf gene, which is crucial in several signalling pathways. Mutations of the newly discovered multiple tumor-suppressor gene (MTS1) on the short arm of chromosome 9 may play a formative role in certain lung cancers. Studies are underway to determine whether genetic alterations occur early or late in tumor progression and whether they are associated with different clinical outcomes.

Although some lung cancers can be inherited, most arise as a result of exposure to environmental or occupational carcinogens. NCI researchers showed that signature molecular lesions or molecular fingerprints reflect exposures to specific agents. For example, certain changes in p53 and ras result from exposure to tobacco-related carcinogens, while other changes are linked to radiation exposure or other causes. Although exposure to radon has been associated with lung cancer in uranium miners, a recent NCI analysis of 1,000 cases of lung cancer in women in New Jersey, Sweden, and China shows no link to residential radon exposures.

Recently completed studies of lung cancer patients in China confirm that smoking is the primary cause of lung cancer in men, although it accounts for only 25 to 35 percent of the cases in women. The lung cancer rates in women are among the world's highest for nonsmokers. The etiologic factors involved remain to be determined, but risk is increased in women who cook with high-temperature rapeseed oils. Chinese researchers have found volatile chemicals released from rapeseed oil to be mutagenic, a finding confirmed by NCI-supported researchers. Lung cancer risk is also increased when indoor coal-burning heaters are used. A study supported by the U.S. Environmental Agency in south China strengthens the observation that heavy air pollution from burning

fossil fuels can, independently of smoking, increase risk of lung cancer

A recent case-control study showed a threefold increase in incidence of lung cancer cases in women when compared to men with equal smoking histories. Hormonal stimulation may contribute to this apparent increased lung cancer susceptibility in women since lung tumors have receptors for estrogen and progesterone NCI-supported scientists are exploring the mechanisms that account for this difference

Currently available screening tools are not effective in reducing mortality from lung cancer. Although lung cancer is often detected on chest x rays taken for other reasons, previous studies have not shown that routine screening in asymptomatic smoking men reduces mortality. The Prostate, Lung, Colorectal, and Ovarian Trial is evaluating the ability of chest x rays to decrease mortality from lung cancer. One anticipated outcome of this trial is identification of biomarkers that can be used to detect early lesions and as intermediate endpoints in chemoprevention clinical trials.

NCI's lung cancer prevention activities include development of educational materials and intervention programs to encourage people to stop smoking or prevent them from starting to smoke. These efforts include the recently completed Community Intervention Trial for Smoking Cessation (COMMIT), and the ongoing effort with the American Cancer Society. state and local health departments, and voluntary organizations to conduct the American Stop Smoking Intervention Study (ASSIST) in 17 states. The results of COMMIT showed that intensive anti-smoking programs increased the rate at which moderate to light smokers quit. However, heavy smokers in the intervention group quit only at the same rate as those in the comparison group.

A broad spectrum of potential chemopreventive agents is under clinical development. These agents include anti-oxidants, anti-inflammatory agents, inhibitors of cell proliferation, and agents that counteract molecules with tumor-promoting activity. The Carotenoid and Retinoid Efficacy Trial is testing the ability of a combination of beta-carotene and retinyl palmitate to reduce lung cancer incidence in high-risk men and women.

The 5-year survival rates for lung cancer remain low. Discovery and development of improved therapies is a high priority for NCI.

Research to identify new genetic and biological markers in blood and sputum that can be used to detect premalignant changes and diagnose lung cancer in early stages is underway. Promising agents being evaluated in NCI-supported clinical trials include cisplatin and VP-16, paclitaxel, navelbine, and neoadjuvant therapy with gemcitabine. NCI-supported scientists continue to search for new drugs and to develop biological and immunotherapies including vaccines.

# Acquired Immune Deficiency Syndrome (AIDS)

HIV infection in women is still increasing. NCI continues studies of the factors involved in transmission of the virus to women and to children of infected mothers. In addition to international epidemiologic studies of women at risk for HIV infection in Italy, Tanzania, Nigeria, Ghana, Jamaica, and Trinidad, NCI sponsors a voluntary international registry of seroconverters. This registry provides data about HIV incubation times and may help identify reasons for male-female differences in HIV infection and disease progression. NCI is also investigating the factors involved in transmission of HIV from pregnant mothers to their newborns. Although various immune mechanisms protect the fetus in utero, their role in preventing infection in newborns is not known. Through the NCI-sponsored International HIV Twins Registry, NCI has found evidence suggesting that exposure to the virus in the vagina during birth could play a significant role in transmission. Based on these findings, NCI and the National Institute of Allergy and Infectious Diseases are designing a clinical trial of inexpensive, widely available solutions to cleanse the birth canal of HIV and lower the risk of infection.

Women are also experiencing an increasing incidence of AIDS-related malignancies. NCI has established a multi-state AIDS/cancer match registry in five areas of the Surveillance, Epidemiology, and End Results (SEER) program. This registry encompasses about 75 percent of all reported AIDS cases and includes 85,000 matches of individuals with AIDS to cancer registries. This registry will serve as an important database for determining the effect of HIV as a co-factor in the development of various cancers, including invasive cervical cancer. In addition, tumor tissue and other

specimens can be obtained for studies to elucidate AIDS/cancer epidemiology.

#### **Initiatives**

#### Conferences and Workshops

- Secretary's Conference To Establish a
  National Action Plan on Breast Cancer
  (December 14, 1993, with the Office of
  Women's Health, Public Health Service)
  The purpose of the meeting was to bring
  together government researchers, academics,
  consumers and advocates, pharmaceutical
  companies, and others to examine all
  aspects of breast cancer and to make
  recommendations. The main goal was to
  establish an action plan to reduce mortality and morbidity due to breast cancer.
- Breast Magnetic Resonance Imaging (MRI)

This workshop reviewed the use of MRI, one of several imaging technologies that shows potential for imaging the breast, and discussed the potential role of this technology in patient management.

- NIH Consensus Development Conference on Ovarian Carcinoma (April 1994)
   The consensus development conference brought together leaders in the field to discuss issues related to screening for ovarian cancer and the optimal management of this disease.
- Cervical Cancer Workshop
  (September 22–24, 1993)
  The program, sponsored by the Organ
  Systems Coordinating Branch, convened
  the researchers involved in all aspects of
  cervical cancer research. Topics included
  molecular biology, immunology, epidemiology, and clinical aspects of cervical
  cancer, allowing a forum of collaborative discussion.
- International Workshop on Screening of Breast Cancer (February 1993)

  Participants in this workshop reviewed the results of several mammography screening studies and looked at issues, such as the rate of false positives and false negatives, and the impact on mortality in women.

#### Requests for Applications (RFA)

• National DES Educational Program for Health Professionals and the Public To improve early detection, diagnosis, and treatment of the medical conditions associated with diethylstilbestrol (DES) exposure, this initiative supports research and education to develop a national program to inform health professionals and the public on the

adverse effects of DES. Educational projects cover topics such as reproductive problems of daughters and sons, cancer risks for mothers and daughters, and other known health risks for DES-exposed offspring.

#### Brcast Cancer Education Summits and Mini-Summits

Through breast cancer education summus and mini-summits. NCI provides support to large cancer research bases to plan, implement, and evaluate education programs on breast cancer. Summits are held to educate and encourage leaders of community organizations, businesses, and health organizations to establish breast cancer education and screening programs, to stimulate access to high-quality mammography, and to encourage establishment of mammography-screening programs where they are needed, especially for underserved populations. The minisummits have similar goals, but are more tailored to the needs of defined target audiences. The meetings were held in 1994 (see workshops).

#### Native-American Women's Cancer Initiative

The goal of this initiative is to improve cancer survival rates in Native-American women through prevention and control efforts. Projects focus on one of three areas: intervention research focusing on cancers more common among or more aggressive in Native-American women; assessment of prevention and control risk factors among these women, including behavioral risk factors (e.g., tobacco use, poor dietary habits); and development of the research capacity of American-Indian and Alaskan-Native women by offering workshops designed to provide technical assistance to increase these groups' research application and scientific skills.

#### Research Project and Development Projects in Chemoprevention

Through these projects, NCI supports translational research in cancer chemoprevention to develop intermediate biomarkers of cancer risk and evaluate the efficacy of biological/molecular markers in chemoprevention trials. The emphasis areas include examining how chemopreventive agents can modulate markers such as cancer genes or their products (e.g., the 17q21 gene associated with breast and ovarian cancers).

#### Collaborative Cancer Prevention Research Units

The Cancer Control Science Program within the Division of Cancer Prevention and Control supports research to identify, evaluate, and implement techniques and approaches for primary and secondary prevention of cancer. The studies may include specific cancers, such as breast and prostate cancer.

#### • Breast Cancer Education Initiatives

The purpose of this RFA is to support new education programs to disseminate information in basic and clinical breast cancer research and intervention practices to a wide range of health care professionals and the lay public, with special emphasis on reaching minority populations

#### Program Projects in Nutrition and Basic Biology Research for Cancer Prevention The Program of the Program

The purpose of this RFA is to encourage research on the role of nutrition in the initiation, promotion, progression, and prevention of cancer and how the findings can be used to develop dietary interventions for the prevention of cancer, with a special emphasis on breast cancer, prostate cancer, and cancer in women and minorities.

#### Phase I and II Trials of New Anticancer Agents

These initiatives will fund clinical trials for promising anticancer agents and laboratory studies that will help elucidate the relationship between drug administration and biological changes in patients. Tumors of special interest include breast, ovarian, and lung cancers.

#### Clinical Correlative Studies in Breast Tumors

This initiative was designed to promote collaboration between clinical and basic science researchers to identify clinical correlations that can improve therapeutic approaches. Studies linked to large clinical trials are encouraged so that markers can be correlated to prognosis and response to treatment in women with breast cancer.

- Development and Evaluation of Minimal Access Surgery in Cancer Treatment
   NCI sponsored this initiative to evaluate the use of minimal access surgical techniques, with the potential to decrease the morbidity, cost, and inconvenience of cancer treatment.
   Solid tumors targeted in the Phase II and Phase III studies include cancers of the ovary, endometrium, and cervix.
- New Therapeutic Approaches for Breast Cancer
   Research to develop novel therapeutic strategies such as gene and vaccine therapy in the treatment of breast cancer will be supported through this RFA.
- Breast Cancer Research Programs in NCI-Designated Cancer Centers (with the National Institute on Environmental Health Sciences (NIEHS) and the National Institute on Aging)
   This effort is designed to stimulate the development of breast cancer research programs in NCI-designated cancer centers.
   The planned program is expected to encourage multiple research approaches to breast cancer involving basic and clinical research and to explore opportunities for prevention and control research when appropriate.
- Patterns of Care in Radiation Oncology
   The objective of this RFA is to focus on
   factors in radiation oncology likely to
   affect patient outcome, such as treatment related morbidity and control of local regional tumors.
- Adult Survivors of Cancer
   Studies supported under this initiative will explore functional and psychosocial issues facing adult cancer survivors, including women with gynecologic cancers. This initiative also supports development of interventions to enhance survivors'

- adaptation to physical impairment, vocational rehabilitation, and psychosocial adjustment.
- Rehabilitation and Psychosocial Research in Younger Women with Breast Cancer (with the National Center for Rehabilitation Research and the National Institute of Child Health and Human Development) The development and testing of interventions that reduce the medical and psychological morbidity and disability associated with the diagnosis and treatment of breast cancer in younger aged women (under age 50) is the focus of this RFA. Among issues of concern for these women are career development, employability, and marriage and family planning.

#### Cancer Pain Management in the Outpatient Setting

The goals of this research initiative are to develop and test interventions to improve the management of cancer pain outside of the acute care or hospice settings, thereby improving the quality of life of persons with cancer living at home or being managed on an outpatient basis. Many patients with bone metastases of breast cancer receive continuing care and maintenance through outpatient and community settings.

- Specialized Programs of Research Excellence in Breast Cancer (SPOREs)
  Breast cancer SPOREs are designed to mobilize laboratory and clinical expertise and to translate basic research findings to clinical and applied innovative research, with the ultimate goal of reducing cancer incidence and mortality and improving survival.
- Cooperative Breast Cancer Tissue Registry
   This initiative seeks to create a network of
   organizations working cooperatively to form
   a registry, which will serve as a resource to
   the research community by improving access
   to archival breast cancer tissue and specimens and associated clinical and outcome
   data for the evaluation of predictive and
   diagnostic markers.

#### Follow-Up of DES-Associated Clear Cell Adenocarcinoma

Awards made under this RFA focus on epidemiologic and interdisciplinary studies to follow patients with DES-associated clear cell adenocarcinoma of the cervix or vagina.

Objectives include surveillance of affected patients; accrual of actual incident cases to document survival, recurrence, second malignancies, and other health outcomes; and collection of data on exposure to DES and other factors

 Interdisciplinary Collaborative Studies in the Genetic Epidemiology of Cancer (with NCHGR)

This RFA is designed to facilitate the cross-disciplinary transfer of technology, methodology, and concepts among epidemiologists, geneticists, laboratory scientists, clinicians, and biobehavioral researchers to advance research on the interaction of genetic and environmental factors in the etiology of cancer. This initiative provides for the study of the genetic epidemiology of cancer in families and populations and specifically encourages studies on breast, ovarian, uterine, and lung cancers

in High-Risk Areas (with NIEHS)
This initiative supports epidemiologic studies to respond to the NCI mandate from the U.S. Senate in Fiscal Year 1993 Appropriations Subcommittee Report to determine the factors contributing to the high breast cancer mortality rates in the Northeastern states. These studies consider known risk factors and focus on markers/indicators of environmen-

tal exposures that may influence geographic

differences and temporal changes in breast

cancer incidence and mortality

**Environmental Factors and Breast Cancer** 

Studies of Genetic Testing and Counseling for Heritable Breast, Ovarian, and Colon Cancer Risks (with NCHGR, the National Institute of Mental Health, and the National Institute of Nursing Research)
 The purpose of this RFA is to examine the

The purpose of this RFA is to examine the psychosocial and clinical impact of using gene-based diagnostic tests in families with heritable forms of breast, ovarian, and colon cancer and to gather information needed to establish clinical protocols for the use of risk-assessment technologies in the future.

 Clinical/Metabolic Studies in Nutrition and Breast Cancer Prevention
 The purpose of this RFA is to encourage interdisciplinary collaborations to develop and conduct clinical/metabolic studies for nutrition and breast-cancer-prevention

• DNA Damage, Genomic Instability, and Breast Cancer

This initiative will support research to establish whether or not there is greater genomic instability associated with individuals in families with hereditary breast cancer than in individuals who do not have a family history of cancer.

- Radiologic Diagnostic Oncology Group V: Stereotactic Biopsy for Non-Palpable Breast Lesion Characterization
  The objective of this initiative is to establish multi-institutional evaluation of imageguided stereotactic breast lesion biopsy and its impact on patient management and cost-effectiveness as compared to open surgical biopsy.
- Breast Cancer Surveillance Research
  Cooperative agreements funded under this
  initiative conduct analytic research to evaluate breast-cancer-screening practices. These
  investigations may include studies of medical
  decision models for workup of women with
  abnormal screening tests, how emerging
  technologies are used, and studies relating
  the biological characteristics of the tumor
  to method of detection.
- The Role of the Microenvironment in Breast and Prostate Cancer
  The purpose of this RFA is to foster the application of recent advances in molecular and cellular biology to study the interactions between tumor and stromal cells and their contributions to malignant progression. The delineation of the genetic and environmental factors involved in stromal-epithelial interactions relevant to progression of hormonally regulated tumors is another research consideration.

#### Program Announcements (PA)

Culturally Sensitive Intervention
 Strategies for Promoting or Implementing
 Compliance with NCI Dietary Guide lines Among African Americans
 Epidemiologic evidence shows a significant
 correlation between diet and specific cancers,
 including breast and colorectal cancer.
 Through this PA, NCI will support research

to develop and evaluate the effectiveness of culturally sensitive intervention strategies to assist African Americans in adopting eating patterns consistent with the NCI Dietary Guidelines.

- Studies on the Prevention, Etiology, Control, Biology, Diagnosis, or Treatment of Breast Cancer This program announcement will expand research support in basic and applied studies of the etiology, biology and immunology, genetic regulation, diagnosis, treatment, assessment of demographics, patterns of care, and strategies for control and prevention of breast cancer.
- Breast Cancer in the Northeastern and Middle Atlantic United States Six studies are evaluating the role of environmental exposures and breast cancer risk in the Northeast and Middle-Atlantic regions of the United States. Data collected by questionnaires are being correlated with and enhanced by quantitative measurements of serum and adipose tissue levels of organochlorine pesticides and PCBs, residential exposure to electromagnetic fields, and serum micronutrient (e.g., vitamin D and antioxidants) determinations. Carcinogenmetabolizing enzymes and genetic polymorphisms are also being characterized to assess the contribution of individual susceptibility to breast cancer risk.
- Genetic and Phenotypic Markers for Ionizing Radiation-Induced Breast Cancer in Rodent and Human Cells The objective of this PA is to encourage studies of the changes of gene expression that are induced by exposure of pluripotent or partially transformed rodent and human mammary epithelial cells to ionizing radiations, and to define the role of such gene sequences in the progression to radiogenic breast cancer in rodent models.
- Federal Technology Transfer Program
  in Digital Mammography
  Digital mammography has been identified
  as the most promising novel technology for
  early detection of breast cancer, offering
  several potential advantages over conventional film mammography. This jointly
  sponsored initiative fosters the development
  of multidisciplinary teams to facilitate technol-

ogy transfer from military to breast-imaging applications and, ultimately, the commercial development of digital imaging systems.

#### Workshops

- Regional Breast Cancer Education
  Summits and Mini-Summits
  Sixteen large-scale regional breast cancer
  education summits and 10 mini-summits
  were conducted by medical centers around
  the country in Fiscal Year 1994. The programs educated leaders of businesses, voluntary and community organizations, and
  health organizations about breast cancer
  and the importance of early detection of
  the disease. Participants were encouraged to
  conduct or sponsor breast cancer education
  and screening activities in their communities. The Susan G. Komen Breast Cancer
  Foundation co-sponsored the program.
- Breast Cancer Education Workshop for Minority Educators (May 20, 1994)
   The aim of this meeting was to encourage minority educators to develop research applications for education grants regarding the causes of cancer, with a particular focus on breast cancer research. A goal of the education programs is to increase the number of biomedical scientists who are members of underrepresented minority populations.
- Workshop on Hereditary Breast,
   Ovarian, and Colon Cancer
   (April 1994, with NCHGR)
   This workshop focused on the review of existing data concerning hereditary breast, ovarian, and colon cancers; discussed the psychosocial and ethical implications of screening for cancers at these sites; and discussed issues related to the development of intervention and prevention strategies.
- Conference on Breast Cancer in Younger Women (January 1993, with ORWH and NICHD)
   This meeting discussed the epidemiology, treatment, and psychosocial issues relevant to young women with breast cancer.
- Breast Cancer Resources To Facilitate Research (September 19-20, 1994)
   The purpose of this meeting was to convene a group consisting of clinicians, basic and clinical research scientists, industrial repre-

sentatives, representatives of the health care industry, consumers, patients, and federal agency representatives to develop and define requirements for national resource banks for biological materials relevant to breast cancer.

- International Conference on Women's
  Health: Occupation and Cancer
  (November 1993, with ORWH, NIEHS,
  and the National Institute on
  Occupational Safety and Health)
  The conference brought together investigators from around the world to describe their work related to gender differences in cancer risk and to identify promising areas of future research. The conference proceedings have been published in three volumes of the Journal of Occupational Medicine
- Determinants of Lung Growth:
  Development Versus Cancer
  (September 1993, with the National
  Heart, Lung, and Blood Institute)
  This workshop reviewed research on normal
  lung development and function Participants
  expect that molecular studies of normal
  lungs may improve our understanding of
  lung cancer development.
- Scientific Progress in Support of Tissue Resources (April 1994)
   The objective of this workshop was to lay the foundation for a national registry of breast cancer biologic materials. Issues addressed included use of peer review to prioritize specimen use, inclusion of normal tissue, and ethical considerations such as informed consent and confidentiality.
- Epidemiology of Hormonal Carcinogenesis (October 1993)
   Participants in this workshop discussed the current state of research about the role of hormones in development of breast, ovarian, and endometrial cancer. An RFA to promote research into the mechanisms responsible for development of cancer was issued as a result of this workshop.

# NATIONAL CENTER FOR HUMAN GENOME RESEARCH

The Human Genome Project is a historic, international research effort that has the goal of analyzing the structure of human DNA and

determining the location and sequence of the estimated 100,000 human genes that constitute the human blueprint. The project evolved from decades of fundamental science research. It is providing researchers with a host of powerful tools and resources to rapidly and efficiently search for disease genes and solve many difficult mysteries of biology and medicine. The resulting acceleration in the pace of gene discovery has been dramatic, with frequent reports in the press of the identification of genes involved in a number of important diseases The identification of the genetic basis of a wide array of diseases will profoundly change the practice of medicine. Disease gene identification leads to diagnostic tests for individuals at risk, which can open the door to effective preventive medicine measures, and ultimately to new cures from innovative drug therapy or gene therapy approaches

In many other ways, as well, the Human Genome Project will provide a powerful stimulus for the biotechnology industry and radically alter the future of biomedical research. NIH and the Department of Energy are the key agencies managing the project in the United States.

The National Center for Human Genome Research (NCHGR) was established in 1989 to lead NIH's effort in the Human Genome Project The NCHGR Division of Extramural Research funds the project's research in laboratories throughout the country. Research in genetic and physical mapping, DNA sequencing, database development, technology development for genome research, and studies of the ethical, legal, and social implications of genetics research are supported by the extramural arm of NCHGR. In February 1993, NCHGR expanded its role at NIH with the establishment of the Division of Intramural Research, focused on applying genome technologies to finding disease genes and developing DNA-based diagnostics and gene therapies. The new division will serve as a hub for human genetics research at NIH, enhancing the work of investigators in other NIH institutes that are searching for specific genes and studying their function in health and disease

#### Accomplishments

Amplified DNA in Breast Cancer Identified Gene amplification, which results in a segment of DNA being repeated, sometimes thousands of times, plays a role in several kinds of solid

tumors. These DNA repeats are believed to occur in up to a third of breast cancer cases. But conventional techniques for examining chromosomes have not been helpful for analyzing such abnormal chunks of genetic material. Scientists at the Laboratory of Cancer Genetics of NCHGR have developed a new strategy for identifying the chromosomal makeup of almost any span of DNA. It is based on microdissection of chromosomes with a tiny glass needle under a microscope, followed by fluorescence in situ hybridization to determine the source of extra genetic material. Using this new technique, the researchers examined DNA from nine different breast cancers. As expected, they found that the most commonly amplified region was derived from the section of chromosome 17 that contains the oncogene ERB-B2; ERB-B2 is almost 10 million bases distant from the newly described BRCA1 gene, which is associated with hereditary forms of breast cancer.

In addition to DNA from chromosome 17, the researchers found amplified DNA from two other chromosomes, 13 and 20, which had not previously been known to contain oncogenes. They also showed that, in more than 80 percent of cases, the amplified DNA was composed of material from at least two chromosome regions. The new technique can help scientists understand how amplified DNA forms and identify chromosome regions that are likely to be amplified in breast cancer.

#### Identifying Mutations in BRCA1

Since the September 1994 announcement that scientists had found a likely candidate for the BRCA1 hereditary breast cancer gene, a number of research groups have been scanning it, seeking specific changes in DNA that may trigger the disease. These studies have borne swift fruit. New reports from researchers in the United States and Canada reveal that susceptible families possess at least 22 different mutations in the very large gene, a discouraging prospect for those who hoped genetic testing for liability to breast cancer might be possible soon. A team of researchers from the University of Pennsylvania and NCHGR described eight possible disease-causing alterations in the gene's DNA among 50 patients with a family history of breast and/or ovarian cancer. The findings also strengthen the scientists' suspicion that BRCA1 is a tumor-suppressor gene. Other researchers in Canada and the United States brought the total number of study families to 100 and the

number of mutations described to 31. Only a few turned up in more than one family, dimming hopes of finding a single mutation that is responsible for a large proportion of early-onset breast or ovarian cancer.

Breast Cancer Gene's Neighborhood Scientists at the NCHGR Laboratory of Gene Transfer have constructed a complex physical map of the region of chromosome 17 that includes BRCA1, the recently identified gene that appears to figure in early-onset familial breast cancer. The physical map describes the genetic "neighborhood" around BRCA1. NCHGR intramural researchers, in collaboration with scientists at the University of Michigan and the University of Pennsylvania, have used the map to isolate at least 26 genes in the region. Seven of these genes appear to be previously unknown. Nineteen, including BRCA1 itself, are either similar or identical to previously identified human genes, or are the human equivalent of genes cloned from other species. Two out of the 19 genes had been cloned previously, but their precise location was unknown. One of the genes that codes for the enzyme glucose-6-phosphatase, which, in mutated form, is responsible for glycogen storage disease type 1a. The other, E1A-f, is a member of an oncogene family.

#### **Initiatives**

In Fiscal Years 1993-1994, NCHGR issued one request for application (RFA) relevant to women's health—RFA HG-94-01: "Studies of Genetic Testing and Counseling for Heritable Breast, Ovarian, and Colon Cancer Risks," in the February 4, 1994, issue of the NIH Guide to Grants and Contracts. The purpose of this RFA was to solicit projects designed to examine the psychosocial and clinical impact of using gene-based diagnostic tests in families with heritable forms of breast, ovarian, and colon cancer; to identify those individuals who have an increased risk of developing cancer and those who do not; to assess public knowledge and attitudes about genetic testing for cancer risks; and to gather information needed to establish clinical protocols for the optimum use of these risk assessment technologies in the future.

The recent isolation of genes that increase a person's likelihood of developing breast, ovarian, or colon cancer brings with it the technological potential for testing large numbers of

people to see if they carry the predisposing genes. DNA testing for susceptibility to some cancers may offer the opportunity for early preventive interventions before invasive cancer develops. At the moment, little is known about the prevalence of predisposing mutations in large populations: the correlation between the presence of the mutations and the development of cancer; the ability of tests to accurately predict risk; or the social, psychological, and economic costs of being tested. Similarly, it is not known how the general population views the use of genetic testing as part of their health care or whether the medical profession is equipped to provide counseling before and after testing NCHGR, the National Cancer Institute, the National Institute of Nursing Research, and the National Institute of Mental Health have jointly awarded more than \$2.5 million to research groups to help answer these questions.

The 3-year grants support 11 research projects in a consortium coordinated by the NCHGR Ethical, Legal, and Social Implications Branch. The researchers will benefit from the consortium format because it will allow them to compare findings along the way on issues common to all projects. In addition, the consortium will reduce duplication of effort in the research and promote sharing of information about informed consent issues and quality assurance of the DNA tests.

# NATIONAL CENTER FOR RESEARCH RESOURCES

The National Center for Research Resources (NCRR) develops and supports critical research technologies that underpin health-related research to maintain and improve the health of the Nation. NCRR supports shared resources, sophisticated instrumentation and technology, animal models for study of human disease, biomedical computing, clinical research, and research infrastructure for underrepresented groups.

Through its support of multidisciplinary research, NCRR is uniquely positioned to provide either primary research support or resource support in partnership with other institutes and centers to address emerging clinical and basic research needs for women's health research. Expansion of NCRR's present efforts in new technologies and instrumentation and development of infrastructure, animal models, and clinical research will foster

interdisciplinary collaborations and advance the efforts of NIH to support research on women's health.

The recent accomplishments in women's health research that are described below exemplify the breadth of science and technology supported by NCRR to promote understanding of normal and abnormal physiology in women and treatment of diseases, disorders, or conditions that are unique to women or have significant impact or manifestations on them. The topics selected include studies of osteoporosis, rheumatoid arthritis, breast cancer, pregnancy and labor, and perinatal HIV infection.

#### Accomplishments

Use of Potassium Bicarbonate To Prevent and Treat Postmenopausal Osteoporosis Using the General Clinical Research Center at the University of California at San Francisco, investigators administered potassium bicarbonate orally for 18 days to 18 postmenopausal women who were given a constant diet. The findings suggest that in postmenopausal women, dietary supplementation with oral potassium bicarbonate in doses sufficient to reduce the net production of endogenous acid reduces the rate of bone resorption, increases the rate of bone formation, and attenuates or reverses the loss of bone in defense of systemic acid-base homeostasis. The long-term administration of potassium bicarbonate may, therefore, be effective in preventing and

treating postmenopausal osteoporosis.

Parathyroid Hormone for the Prevention of Bone Loss Induced by Estrogen Deficiency Analogs of gonadotropin-releasing hormone (GnRH) are often given to induce hypogonadism in women who have estrogen-dependent disorders, such as endometriosis and uterine leiomyomas. Because estrogen deficiency causes bone loss, concerns about premature osteoporosis have prevented long-term therapy with GnRH analogs. In a study conducted on the General Clinical Research Center at the Massachusetts General Hospital, serum estradiol concentrations fell to postmenopausal values in 36 of the 40 women enrolled. In the women who received the GnRH analog nafarelin alone, the mean bone density in the lumbar spine decreased. In contrast, bone density in the lumbar spine did not change when measured in the anteroposterior projection and increased when measured in the lateral projection in women who also received the parathyroid hormone. Bone density at the femoral neck decreased slightly in both groups. Radial bone density did not change in either group. Serum alkaline phosphatase and osteocalcin concentrations and urinary hydroxyproline and pyridinoline excretion increased in women who received nafarelin plus the parathyroid hormone, indicating that the parathyroid hormone can prevent bone loss in the lumbar spine in young women with estrogen deficiency caused by treatment with GnRH analogs.

#### Relationship of Teenage and Current Calcium Intake to Bone Mineral Density of the Hip and Forearm in Women Aged 30 to 39 Years

The relationship between diet and bone mineral density (BMD) in premenopausal women was evaluated in a cross-sectional study of 139 women aged 30 to 39 years at the Columbia University General Clinical Research Center. A food frequency questionnaire was used to determine nutrient intake for both the year prior to BMD measurement and for ages 13 to 17 years. Physical measurements included height, weight, grip strength, and percent body fat. BMD was measured in the lumbar spine, hip, and forearm. Multiple regression equations were used to relate nutrient intake to BMD while controlling for age, height, weight, and grip strength. There was no relation between lumbar spine or distal forearm BMD for any nutrient studied from either the current or teenage diet. Current dietary calcium intake was modestly related to hip BMD, and adding fiber intake to the multiple regression model strengthened the association between calcium and BMD. This would be expected because fiber interferes with calcium absorption. In the teenage diet, phosphorus and calcium were related to hip BMD. A higher lifetime calcium intake was associated with a higher hip BMD compared with a low lifetime calcium intake. An increase in teenage calcium intake from 800 to 1200 mg per day is estimated to increase hip BMD by 6 percent.

#### Therapy for Rheumatoid Arthritis

Using General Clinical Research Centers resources at the University of Alabama, investigators have conducted a randomized, double-blind placebo-controlled study to determine the effect of two different weekly doses of folic acid, an inexpensive vitamin, on the toxicity

and efficacy of low-dose methotrexate therapy for rheumatoid arthritis. In other studies, dose response-related toxic effects have been reported in 30 to 90 percent of patients given methotrexate, a folic acid antagonist. Toxic effects include gastrointestinal intolerance, hematologic abnormalities, alopecia, and pulmonary toxicity. The investigators at the University of Alabama conclude that folic acid is safe in a broad range of doses and protects patients with rheumatoid arthritis who are taking methotrexate from toxicity while preserving the efficacy of methotrexate.

# Identification of the Breast Cancer Susceptibility Gene

The major recent advance in breast cancer research was the identification of the breast cancer susceptibility gene, BRCA1. The publication reporting this discovery (Science, 266, pp. 66-71, October 7, 1994) cites support from a number of NIH grants including the University of Utah General Clinical Research Centers grant. The kindreds reported in this landmark paper were evaluated at the Utah General Clinical Research Center, and these individuals are continuing to be studied there. The General Clinical Research Center Core Laboratory was involved in generating the cell lines from which the DNA was extracted for the mutational analysis. The objective of a follow-up study is to investigate the psychological impact on subjects who learn they have a BRCA1 mutation and thus are susceptible to the development of breast cancer.

#### Magnetic Resonance Imaging Diagnosis of Breast Lesions To Avoid False Negative Biopsies

Investigators at the University of Pennsylvania, Department of Radiology, have a great interest in high-resolution magnetic resonance imaging (MRI) of breast lesions as a follow-up procedure to mammography. The hope is that with high enough resolution, the soft tissue contrast of MRI will allow specific diagnosis and help to reduce the large number of false negative breast biopsies that are performed each year. Investigators have designed special receiver coils and customized gradient sets for higher resolution. They currently are able to image breast lesions at approximately 200 micron resolution, are identifying architectural features of these lesions that correlate with specific diagnoses, and are currently developing diagnostic feature sets. At present, the images of a benign breast tumor called a fibroadenoma, when collected at 200 micron resolution, allow a specific diagnosis to be made. Researchers hope that MRI can be used noninvasively to diagnose breast lesions and avoid false negative biopsies. These studies are supported by the Biomedical Research Technology Program.

#### Role of Proteins in Breast Tumors

Calmodulin is a protein known to play a central role in calcium-dependent signaling in cells where it mediates functions, such as muscle contraction, hormone secretion, and cell division. A protein very similar to calmodulin has recently been identified. Unlike calmodulin, the levels of this protein in human breast tumors are at least 50 times lower than in normal breast tissue. A study of the structure of this protein alone and complexed with a wellknown calmodulin antagonist, trifluoroperazine, is to be carried out by using the synchrotron resource, supported by the Biomedical Research Technology Program at Stanford University. Trifluoroperazine is currently being evaluated for its effectiveness in breast cancer treatment. This basic structural study may help explain the role of this new protein in normal and cancerous breast tissue and could suggest new drugs for treatment.

#### Molecular Biology Studies of Human Relaxin and Relaxin-Like Genes

Relaxin, a polypeptide hormone, has historically been associated with the loosening of the pelvic ligaments and dilatation of the cervix necessary for the safe delivery of the fetus. Recent work in humans has shown that relaxin may have additional roles in different tissues at different developmental stages. Work is in progress on the role of relaxin during the later stages of pregnancy leading to the timed rupture of the fetal membranes and its role regarding the placenta during pregnancy.

An investigator, supported by a Research Centers in Minority Institutions grant, at the University of Hawaii at Manoa has recently published a paper demonstrating that the two relaxin genes H1 and H2 are expressed in normal and neoplastic breast tissues. In neoplastic breast tissue, the H2 relaxin gene is more highly expressed than in the normal breast tissue. Positive immunohistochemical staining for relaxins has confirmed that the proteins are

present in these tissues. The staining in neoplastic breast tissues is more intense than its comparable normal postmenopausal counterpart. Experiments are now being conducted to determine the role of relaxins in neoplastic breast tissues. Other investigators have shown that relaxins increased the level of enzymes responsible for degradation of the matrix around cells (extracellular matrix). Because cancer is associated with the invasion of the surrounding tissues, it is important to determine if relaxin has a role in the degradation of the extracellular matrix leading to invasion of the surrounding tissues by the cancerous cells.

Concurrent with the work on relaxin and neoplastic breast tissues, a new gene has been uncovered in the ovary and placenta. A recent publication has shown that an insulin-like, relaxin-like gene, hLeydig I-L, was present in the male. Because of the structural similarity of this new gene with human relaxins, work was initiated to determine if this gene is present in the female. By using molecular biology techniques, such as polymerase chain reaction, cloning, and sequencing, it has been demonstrated that this hLeydig I-L gene is expressed in the human ovary and placenta. The significance of this finding has yet to be determined.

#### Prevention of Premature Labor

Prematurity and related complications (respiratory distress, hyaline membrane disease, and intracranial hemorrhage) are the most frequent preventable causes of neonatal loss. Researchers at the California Regional Primate Research Center are evaluating an oxytocin antagonist commonly used to prevent premature labor. Results indicate no significant treatment-related effects on the mothers or infants. This antagonist, and related compounds, shows promise for use in women at risk for premature labor and delivery.

#### Control of Parturition

Investigators at the Oregon Regional Primate Research Center are studying factors that control the onset of parturition. They have found that pregnant rhesus monkeys show circadian changes in plasma oxytocin concentrations and that these changes are responsible for nocturnal uterine activity episodes. Estrogens may modulate these effects. This group has also made substantial progress in developing an animal model in the pregnant rhesus monkey to study the role

of bacterial infections in bringing about premature birth.

Relationship of Hypoxia to Preeclampsia Preeclampsia is a frequently occurring, serious complication of pregnancy that can severely harm both the mother and the baby. Little progress has been made in understanding the causes of this condition. In normal pregnancy, fetal cytotrophoblasts invade maternal (uterine) arterioles, thus bringing oxygenated blood to the placenta. In preeclampsia, cytotrophoblast invasion is abnormally shallow, and the cells become hypoxic (oxygen-deprived). Current data suggest that the symptoms experienced by the mother, such as proteinuria and malignant hypertension, are caused by toxic factors released by these hypoxic cytotrophoblasts.

Investigators at the Bio-Organic Biomedical Mass Spectrometry Resource supported by the Biomedical Research Technology Program have developed an in vitro model that allows comparison of proteins produced by cytotrophoblasts under normal and hypoxic conditions. In the first phase of this study, proteins were separated from conditioned media and cell lysates by two-dimensional gel electrophoresis. By using this method, under hypoxic conditions, seven discrete proteins were observed to increase in production fivefold and one protein to decrease. Mass spectrometry is now being used in the second phase of this study to determine the structure and sequence of these proteins isolated from the gels. Knowing the identification of these proteins will be a key factor in determining their physiological role in the etiology of preeclampsia.

# Effect of Congenital or Perinatal Infection With HIV on the Development of the Immune System

The incidence of HIV infection in women and infants is increasing, especially in black and Hispanic populations. The estimated rate of mother to infant transmission is 15 to 30 percent without azidothymidine (AZT) prophylactic intervention during pregnancy. The early diagnosis of HIV infection continues to be difficult. It is complicated by the presence of maternal antibodies in the infant's circulation and by asymptomatic presentation at birth.

Scientists at Meharry Medical College are investigating the impact of HIV infection on the immune system of HIV-positive mothers and their newborn children in a longitudinal,

retrospective pilot study supported by the Research Centers in Minority Institutions Program. They have developed a clinical research coordinating agency called Project SHARE (Specialized Healthcare Aimed at Research and Education), which serves as a referral site for HIV-infected women in Nashville and the surrounding counties. In addition to coordinating patient clinical research contact with research protocols, Project SHARE provides HIV-specific counseling, education. and service to research participants to address their needs and their families' needs. It is also an effective tool for subject recruitment and retention. In an area where HIV infection in the heterosexual population and in women is lower than in areas such as New York City, 32 women and their babies have been recruited into the study. Of these, 24 women are infected and 8 serve as a control group; 70 percent of the infected women and 80 percent of the control women are black.

Investigators are using several means of assessing the status of the immune system in women: (1) tracking the levels of various lymphocyte subpopulations that may change as infection progresses, (2) assessing the ability of the lymphocytes from these mothers to respond to various stimuli in an effort to link lymphocyte subset numbers with their function, and (3) investigating the ability of these cells to produce and respond to cytokines that have been associated either with immune function or with changes in disease status.

#### **Initiatives**

NCRR did not issue any specific Requests for Applications, Requests for Proposals, Program Announcements, or workshops in the area of women's health issues in Fiscal Years 1993 and 1994. However, NCRR contributes a significant portion of its budget to health and behavior research. The demand for the Center's resources determines scientific and funding shifts. Therefore, future increases in women's health and behavior research supported by other components of NIH will result in corresponding NCRR increases.

#### NATIONAL EYE INSTITUTE

The National Eye Institute (NEI) was created on August 16, 1968, by Public Law 90-489 with the mission to conduct and support research, training, health information dissemi-

nation, and other programs regarding blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of blind persons.

The major causes of blindness (glaucoma, macular degeneration, diabetic retinopathy, uvertis, and cataract) affect both women and men. However, because women live longer than men do on average, more women than men are affected by these age-related eye diseases in the United States. In addition, there appears to be a small excess risk of cataract and macular degeneration for women over that of men.

Several eye conditions affect women significantly more frequently than men. These conditions are optic neuritis, a demyelinating disease of the optic nerve that may be a precursor of multiple sclerosis; dry eye, a common condition that is associated with decreased tear secretion that in most cases causes mild discomfort but in more severe cases may result in corneal scarring and blindness; and Sjogren's syndrome, an autoimmune disorder that results in severe ocular surface alterations, including decreased aqueous tear production, squamous metaplasia, goblet cell loss, and lymphocytic infiltration.

#### Accomplishments

#### **Optic Neuritis**

Optic neuritis is an acute debilitating inflammation of the optic nerve that affects more that 25,000 Americans each year, primarily women between the ages of 18 and 45. People with this disease usually have rapid vision loss and ocular pain. The NEI-supported Optic Neuritis Treatment Trial (ONTT) compared oral corticosteroid, intravenous steroid followed by oral corticosteroid, and placebo for the treatment of new cases of optic neuritis. Results from the ONTT showed that oral corticosteroid, the most common treatment of the disease, when used alone is ineffective in treating the disease and actually increases a person's risk for future attacks; whereas intravenously administered corticosteroids promoted more rapid recovery and did not increase the rate of recurrence. Based on data collected from 2 years of followup of patients enrolled in the ONTT, researchers found that treating first-time optic neuritis patients with a combination of intravenous and oral corticosteroids lowers their risk of developing multiple sclerosis. The results from this

research, published in the *New England Journal* of *Medicine*, offers the first scientific evidence that intravenous corticosteroids help to delay the progression of multiple sclerosis

Recently, NEI-supported scientists have shown that naturally occurring hydrogen peroxide in the central nervous system can be detoxified by polyethylene glycol catalase in experimental optic neuritis in animals. These results indicate that detoxification of endogenous hydrogen peroxide may be an effective treatment for preventing demyelination in the central nervous system from disorders such as optic neuritis and multiple sclerosis.

#### Dry Eye

Dry eye is a common condition that is associated with a decrease of tear secretion. In most cases, dry eye causes mild discomfort, but in some individuals this disease may lead to damage and scarring in corneal tissues that may ultimately cause blindness. Although it affects both men and women, dry eye is more prevalent in women over the age of 45, and it can occur in association with Sjogren's syndrome, a systemic disease that primarily affects women Investigators hypothesize that reproductive hormones regulate lacrimal gland secretion and that disturbances in this regulation can lead to tear film insufficiency. In support of this hypothesis, the results of recent research suggest a key role for prolactin in the development of gender-related differences in lacrimal gland function. Prolactin has been shown to inhibit normal tear secretion. Prolactin inhibition of tear production may be much more pronounced in postmenopausal women; research has shown that estrogen enhances prolactin synthesis, while androgens inhibit the production of prolactin. Therefore, prolactin inhibition of tear production may be more pronounced in postmenopausal women, and dry eye could be exacerbated in women who are treated with estrogen without androgens.

#### Sjögren's Syndrome

Sjögren's syndrome is an autoimmune disease that results in severe ocular surface alterations and decreased aqueous tear production. The mechanisms responsible for the pathological processes manifested in Sjögren's syndrome are not well understood. Researchers supported by NEI are exploring the role of the Epstein Barr (EB) virus (the herpes virus that causes infectious mononucleosis) in the pathogenesis of

this disorder. In situ DNA hybridization studies have shown that primary infection with this virus develops into a persistent and latent infection in tear duct epithelial cells in approximately 35 percent of the people who have contracted the EB virus. Viral DNA is present in these latent infections, but no viral protein production could be detected. In Sjögren's patients the EB virus induces proliferation of B-lymphocytes in the lacrimal glands and infects the majority of ductal epithelial cells. Thus, virus infection may be a risk factor for the development of ocular Sjögren's syndrome symptoms, and antiviral agents may have therapeutic potential for treating this most severe type of dry eye condition.

#### Idiopathic Macular Holes

Idiopathic macular holes, a disease that affects more women than men, frequently result from the formation of a cyst on the macula; data from the NEI-funded Eye Disease Case-Control Study indicate that higher fibrinogen levels and a history of glaucoma were also associated with an increased risk for this condition. The use of exogenous estrogens was associated with a decreased risk for macular hole development. Macular holes often cause a degradation of visual acuity to 20/200 or less. The NEI-supported Vitrectomy for Macular Hole Follow-Up Study will evaluate the long-term benefits of surgical intervention in the treatment of macular holes and hemorrhagic macular degeneration, and determine the incidence of surgical complications and the relationship of these complications to visual acuity outcome.

#### Strabismus

Recent evidence suggests that children who are born to mothers who smoked cigarettes during their pregnancies may be at greater risk for developing strabismus. A population-based case-control study was conducted at nine pediatric ophthalmology centers that evaluated all incident cases of strabismus diagnosed during a 21-month period from 1985 to 1986 in Baltimore. The study found an association between cigarette smoking during pregnancy and inward deviations (esotropia), but not outward deviations (exotropia), of the fixating eve. The study also found that maternal smoking was a risk factor for strabismus in low birth weight babies and babies in the upper half of the birth weight distribution.

#### Diabetic Eye Disease

Diabetic retinopathy is one of the most important causes of visual loss, accounting for approximately 12 percent of new cases of blindness each year in the United States. Diabetes increases the risk of blindness 25-fold over that of the general population, and it is estimated that 24,000 Americans become blind each year as a result of diabetic eye disease. In addition to supporting basic research for diabetic eye disease, NEI, through the National Eye Health Education Program, is conducting public and professional education activities that stress the importance of early detection and timely treatment of diabetic eye disease. NEI has recently inaugurated a study that will evaluate the efficacy of an inexpensive educational intervention to promote annual ophthalmic screening for low-income black women.

#### **Initiatives**

NEI and the National Eye Advisory Council have established, in *Vision Research—A National Plan: 1994–1998*, goals, objectives, and research priorities for improving visual health and preventing blindness, including diseases that have a higher incidence and prevalence for women than for men. NEI's current research projects include the following:

#### · Optic neuritis

A goal of the NEI research plan is to develop an animal model of this disease to better understand the pathogenesis of the disorder and to understand the relationship between optic neuritis and multiple sclerosis.

Sjögren's syndrome and dry eye
 NEI is supporting research to determine
 the role of sex hormones on lacrimal gland
 function, specifically the effect of prolactin
 on the synthesis of androgen. This project
 will increase our understanding of hormon ally mediated, lacrimal insufficiency in post menopausal women, pregnant women, and
 women who are taking oral contraceptives.

#### · Breast cancer

NEI is supporting research on the genetic relationship between retinoblastoma, a potentially deadly inherited cancer of the eye in young children, and the initiation and progression of malignant tumors in the breast.

# NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national program in diseases of the heart, blood vessels. lungs, and blood, in the uses of blood and the management of blood resources, and in sleep disorders. The diseases that fall within the NHLBI mandate constitute major health concerns for both women and men in the United States. Heart disease, cerebrovascular disease. and chronic obstructive pulmonary disease are the first, third, and fourth most common causes of death in the United States. Many other conditions of interest to the Institute (e.g., hypertension, asthma, sickle cell anemia, and cystic fibrosis) exact a large toll in terms of the burden of illness and health care costs.

NHLBI supports a range of both observational and interventional studies to identify and elucidate gender differences in manifestations, diagnosis, prognosis, treatment, and risk factors related to diseases within its purview. In addition, the Institute has a significant portfolio of studies focused entirely on women to improve understanding of how such factors as age, life stage, race/ethnicity, socioeconomic status, lifestyle, and psychosocial influences affect women in health and illness.

#### Accomplishments

#### Postmenopausal Estrogen/Progestin Interventions Trial

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial—the first major clinical trial to examine the effects of hormone replacement therapy (HRT) on coronary heart disease (CHD) risk factors in postmenopausal women -found that all four of the hormonal regimens tested produced significant increases in levels of high-density lipoprotein (HDL) cholesterol. For women, a high level of HDL cholesterol is believed to provide strong protection against CHD. Although estrogen taken alone and estrogen combined with micronized (natural) progesterone yielded the greatest increases in HDL cholesterol, the two other estrogen/ progestin combinations tested also compared favorably with a placebo. The PEPI study also found that, compared with the placebo, all of the active treatments caused significant decreases in harmful low-density lipoprotein (LDL) cholesterol and fibrinogen, a blood

clotting factor predictive of stroke and heart attack. Furthermore, neither estrogen taken alone nor the estrogen/progestin combinations increased blood pressure, as had been previously believed.

Study participants who had not had a hysterectomy underwent annual biopsies to detect cell overgrowth in the uterine lining, a potentially harmful condition. Although none of the three estrogen/progestin combinations caused this condition, more than half of the women taking estrogen alone experienced it. These results indicate that combination HRT may be the preferred treatment for women who have a uterus. The results of the PEPI study provide scientifically based guidance for postmenopausal women and their physicians seeking safe hormonal regimens that will improve their CHD risk factors.

### Estrogen Replacement Therapy (ERT) in Elderly Women

The relationships between ERT, cardiovascular disease risk factors, and carotid atherosclerosis were recently examined in a large sample of older women. Current use of ERT was reported by 12.5 percent of 2,955 women aged 65 to 100 years in the NHLBI Cardiovascular Health Study, and past ERT use was reported by an additional 26 percent. ERT, either past or current, was strongly associated with younger age, lower levels of LDL cholesterol, glucose, insulin. fibrinogen, and obesity; higher levels of HDL cholesterol; and higher socioeconomic status effects that tended to be greater in current users than in past users ERT users also had lower carotid intimal-medial thickness and carotid stenosis grade, measures of atherosclerosis. The findings suggest that the cardiovascular benefits of ERT may be realized even many years after menopause has taken place

#### Vitamin E Consumption and Risk of CHD

A study of 87,245 women nurses who were 34 to 59 years of age and free of CHD in 1980 found that those who took vitamin E supplements for at least 2 years experienced a 41-percent reduction in CHD risk. The study took into account other major risk factors for CHD, including age, smoking habits, dietary nutrient intake, and consumption of other types of antioxidants in addition to vitamin E. Women in the highest 20 percent of vitamin E consumption had two-thirds the risk of major CHD of those in the lowest 20 percent.

Although these observational data do not prove a cause-and-effect relation, they suggest that among middle-aged women, the use of vitamin E supplements is associated with a reduced risk of CHD. Public policy recommendations about the widespread use of vitamin E await the results of randomized clinical trials of primary and secondary prevention of CHD.

Angiographic Trial for Prevention of CHD A new study in postmenopausal women will evaluate the separate and combined effects of HRT and antioxidant vitamin treatment on coronary artery lesions in women. Although the onset of CHD occurs at a later age in women than in men, over the entire life span CHD is the single most important cause of mortality in women. Furthermore, once women show clinical signs of CHD, their prognosis is poor and often worse than that for men. Thus, prevention is a high priority. Angiographic trials in men have demonstrated that it is possible to stabilize atherosclerotic lesions, inhibit their progression, and induce their regression. Even relatively modest angiographic changes have been associated with substantial reductions in clinical cardiovascular events. Limited available data suggest that the same may be true for women. The new NHLBI study is expected to identify therapeutic options and increase understanding of CHD in women. The HRT component of this trial complements results of the PEPI study.

#### Atherosclerosis in Young Women

Evidence from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study indicates that atherosclerosis begins early in life in women, as well as in men. Other studies have found lesions in the aortas of children as young as 3 years of age that are believed to progress in early adulthood and set the stage for later development of clinical CHD. PDAY collected arteries, blood, and other tissues at autopsy from 2,500 young victims of accidental death, 668 of whom were women. Lesions were found in all of the aortas and about half of the right coronary arteries in the youngest group of women (15 to 19 years of age), and the amount of artery surface affected increased by as much as sevenfold as age increased from 15 to 34 years. The extent and prevalence of raised lesions in the aorta and the right coronary artery also increased with age. Lesion severity correlated with cigarette smoking, high LDL and low HDL cholesterol levels, obesity, diabetes, and hypertension. The study provides important evidence that lesion progression in young women is influenced by the same risk factors that operate in adult women. It strongly supports the recommendations of the National Cholesterol Education Program (NCEP) regarding healthy diets to lower cholesterol for females (as well as males) over 2 years of age and also emphasizes the importance of efforts to control hypertension, diabetes, and obesity at a young age.

#### Diet and Risk Factors for Atherosclerosis

The Dietary Effects on Lipoproteins and Thrombogenic Activity (DELTA) study examined the effects of dietary fat modification on atherosclerosis risk factors. Prior studies of the effects of diet on cholesterol levels and fat metabolism had been conducted with small numbers of subjects and, as a consequence, were unable to assess whether women differed from men in their responses to dietary interventions. For a period of 6 months, DELTA provided meals with exactly 5, 9, or 16 percent of daily calories from saturated fat to more than 100 healthy adults, 60 of whom were women, including a relatively large number of premenopausal, younger women. Women and men were found to have similar lipid and blood-clotting-factor responses to the experimental diets, which suggests that women may benefit from some of the same interventions used in men to reduce risk of atherosclerosis.

Another NHLBI-supported study is evaluating gender differences in the effects of diet on lipid lowering in high-risk persons. Researchers are assessing the lipid-lowering response to the NCEP Step Two diet in women and men with hyperlipidemia. This is the first large-scale, industry-based study of adherence of women and men to the NCEP Step Two dietary guidelines. If the results show that women differ from men in their ability to adhere to or respond biologically to the diet, it may be important to develop new dietary therapeutic approaches tailored specifically to women.

#### Body Weight and Risk of CHD

Research findings from a longitudinal study indicate that even a mild amount of excess weight increases a woman's chances of developing CHD. The study involved 115,818 women aged 30 to 55 years in 1976 who had no history of CHD. During 14 years of follow-up, investigators found that women who were overweight

and had gained weight since the 18th birthday had the greatest risk of developing CHD. Using the body mass index (BMI) as a measure of obesity, current U.S. guidelines define the normal range as a BMI of 21 to 27 kg/m<sup>2</sup> (e.g., 124 to 170 pounds for a 5-foot, 6-inch woman). The study found that women whose BMI was in the range of 23 to 27 kg/m<sup>2</sup> (145 to 170 pounds for a 5-foot, 6-inch woman) had an estimated 31-percent increased risk of CHD in comparison with women whose BMIs were below this range. This finding suggests that current guidelines may provide false reassurance to a large number of women who are not overweight according to the guidelines but who have a weight-related increased risk of CHD

#### Obesity in Adolescent Girls

The high prevalence of obesity among black women may contribute to the high rate of cardiovascular disease (CVD) morbidity and mortality observed in this population. To gain a better understanding of this phenomenon, the NHLBI Growth and Health Study investigated the development of obesity and associated CVD risk factors in black girls and white girls, beginning at 9 to 10 years of age. At that age, black girls were taller, heavier, and more sexually mature and had higher body mass index, more body fat as measured by skinfold thicknesses, and higher blood pressure than white girls. Blood lipid profiles were more favorable in black girls than in white girls, with HDL cholesterol higher and triglycerides lower. In girls of both races, puberty was associated with increases in body fat and blood pressure and decreases in LDL cholesterol and triglycerides. Beginning at age 12, there was a greater increase in deposition of body fat in black girls than in white girls. Behaviors related to adiposity at baseline included dietary fat intake and television-watching. The important results of this program will provide guidance for developing interventions for the prevention of obesity.

# Activity Counseling Trial (ACT) To Reduce CVD Risk

Physical activity can reduce blood pressure, prevent hypertension, increase HDL cholesterol, and reduce obesity. Unfortunately, the majority of the U.S. population is sedentary, women more so than men. The ACT study was initiated in 1994 to test two different

interventions in primary care clinical practices to encourage sedentary adults to become more active. The interventions are directed toward women and men who are at high risk for CVD because of elevated blood pressure or blood lipid levels. Because the effectiveness of various interventions may be different in women and men, the study is designed to test them separately in the two genders. Its results are expected to lead to effective intervention strategies for use in clinical settings to help women become more physically active, thereby reducing CVD risk.

### Sodium Imbalance and Hypertension in Black Women

The prevalence and severity of hypertension are considerably greater among black women in the United States than among white women. Alterations in renal function, particularly with regard to the handling of sodium and other electrolytes, may underlie a large percentage of the hypertension seen in blacks. One possible defect that may account for this phenomenon is altered function of an enzyme known as Na, K-ATPase, which is responsible for maintaining correct cellular levels of sodium and potassium. Interestingly, depressed activity of Na, K-ATPase seems to be common in black women Investigators are now beginning to test the hypothesis that products of an important enzyme system known as cytochrome P-450 may form chemicals that can alter sodium pump activity and, therefore, the amount of sodium in the body Theoretically, alterations in pump activity trigger a cascade of events that ultimately lead to hypertension. This hypothesis is being tested in normotensive and hypertensive women The studies are expected to yield important information about racial and ethnic patterns of blood pressure regulation and enhance understanding of the genetic basis of salt-sensitive hypertension in black women. An additional benefit may be the design of specific therapeutic approaches for control of salt-sensitive essential hypertension.

#### Diagnostic Strategies for CHD

The NHLBI-supported Evaluation of Ischemic Heart Disease in Women Study will address the problems of differential utilization of invasive cardiovascular procedures in women and men. In general, women undergo fewer diagnostic and therapeutic procedures (e.g., angiography, thrombolytic therapy, coronary bypass surgery,

and angioplasty) than men. Among the problems related to diagnostic evaluation of women suspected of having CHD is the fact that symptom recognition and diagnostic methods validated in men have been less useful for women; this observation may have negatively influenced the decision to evaluate symptomatic women. The new study, scheduled to start in 1995, will focus on the identification of clinically useful methods to identify women with CHD. Reliable methods for early identification of such patients will assist physicians in determining appropriate treatments for women at risk.

#### Prognosis After Onset of CHD

Women and men in the Framingham Heart Study who developed clinically apparent CHD between 1951 and 1986 were compared to detect gender differences in prognosis according to CHD presentation. The manner of CHD presentation, which included angina, coronary insufficiency (unstable angina), recognized myocardial infarction (MI), unrecognized MI, and coronary death differed between men and women. Men were most likely to present with MI, whereas women tended to present with angina. Following onset of angina, men were at greater risk than women for MI and coronary death after age and CHD risk factors were taken into account. There was a trend toward greater overall mortality in women than in men after a recognized MI; however, men were at higher risk for death than women after an unrecognized MI. Further research is exploring the reasons for these gender differences, with the goal of developing approaches to improve survival in women and men with CHD.

### Rapid Early Action for Coronary Treatment (REACT)

Some studies have reported that women delay longer than men in seeking medical care for symptoms of acute MI (AMI), perhaps because their symptoms are often not obviously cardiac in nature. Recognizing the importance of early treatment for AMI to lower morbidity and mortality, the REACT program is testing, in 20 U.S. communities, an innovative educational program for reducing delay time in seeking medical care for symptoms of AMI. Media messages and educational approaches addressed specifically to women will be developed based on studies that have reported characteristics of AMI symptoms in women and on results of women's focus groups conducted by REACT.

The effects of educational interventions on delay time in women compared to men will be examined, as will the effects on AMI severity and death rates. The study is expected to provide insight into reasons for treatment delay by women and to result in effective community-based educational approaches to decrease delay time, thereby reducing death rates from AMI.

#### Outcome of Coronary Angioplasty

Women who participated in the NHLBI Percutaneous Transluminal Coronary Angioplasty (PTCA) Registry from 1985 to 1986 were found to have more procedure-related complications and greater inhospital mortality than men. Although the higher rate of in-hospital complications in women is not fully understood, it may be attributable to the fact that the women were older; had higher cardiovascular risk, including more frequent history of congestive heart failure; had a greater prevalence of hypertension; and were considered to be at high surgical risk twice as frequently as were men. Women also were more likely to have diabetes or unstable angina at the time of referral for angioplasty. Despite their poorer risk factor profile, however, the women's inhospital complication and mortality rates were still quite low. Furthermore, successful PTCA improved long-term survival for women and was associated with a lower incidence of subsequent restenosis and revascularization than in men. These findings support the use of PTCA for women in need of coronary revascularization.

# Biobehavioral Characteristics of Bypass Patients

A number of studies have documented poorer physical and psychosocial profiles for women who experience MI and who undergo coronary artery bypass graft (CABG) surgery, relative to men. The Post-CABG Biobehavioral Study, a prospective assessment of psychosocial functioning in 759 patients undergoing CABG surgery, confirmed this observation. Women in the study were more likely than men to be unmarried and old and to have less education and lower incomes. In addition, women were found to be in poorer health prior to surgery than men: among patients selected to participate in the study, 16 women (2.8 percent) versus 4 men (0.5 percent) died prior to being enrolled, and women who were enrolled were more likely than men to have severe angina, to be in the coronary care or intensive care unit,

and to be scheduled for CABG surgery on the same day as cardiac catheterization. Relative to men, women undergoing CABG surgery were also found to be more depressed and anxious at the time of surgery, to rate their satisfaction with life at a lower level, and to have poorer social and physical functioning. These findings shed important light on the design of interventions to address the special medical and psychosocial needs of women who undergo CABG surgery.

#### Calcium Supplementation to Treat Hypertension in Pregnancy

A new clinical trial in pregnant hypertensive women is investigating the use of oral calcium supplementation to reduce blood pressure. need for antihypertensive drugs, and incidence of pregnancy-associated cardiovascular complications. Hypertensive women who become pregnant are more susceptible to serious maternal and fetal complications than are women who have normal blood pressure. Moreover, such women are often treated with antihypertensive drugs whose safety in pregnancy has not been established and whose efficacy in preventing many of the complications of high blood pressure during pregnancy is questionable. The new study is assessing hemodynamic, hormonal, and biochemical variables, as well as cardiovascular risk factors, such as hypertension, obesity, and hyperlipidemia. Results are expected to lead to improved treatments for hypertensive pregnant women and better understanding of the mechanism by which calcium may exert its beneficial effects.

#### Pregnancy and Subsequent Risk of CVD

The association between the number of pregnancies and CVD in women who had completed childbearing was tested in 2,356 women followed for 28 years through the Framingham Heart Study and 2,533 women followed for at least 12 years through the first National Health and Nutrition Examination Survey National Epidemiologic Follow-Up Study. When age and educational level were taken into account, rates of CHD were higher among women who had many pregnancies than among women who had never been pregnant. In both studies, however, the higher rates were statistically significant only for women with six or more pregnancies. Adjustments for other known CVD risk

factors, including weight, did not markedly alter this risk. Whether some aspect of pregnancy itself or another unmeasured factor accounts for the increase in observed risk requires further investigation.

#### Raynaud's Treatment Study (RTS)

Epidemiological evidence suggests that the incidence of primary Raynaud's phenomenon is twice as common in women as in men. The RTS is a randomized clinical trial of pharmacological and nonpharmacological treatments for Raynaud's phenomenon to determine the best therapies and, most particularly, to shed light on the efficacy and duration of benefit from a course of temperature biofeedback treatment-The study will compare temperature biofeedback with three other treatments (muscle tension biofeedback, active medication, and placebo) in terms of their effects on selfreported Raynaud's attacks. Final results, expected in late 1996, will be important in determining appropriate treatment strategies for patients with Raynaud's phenomenon.

#### Health Benefits of Smoking Cessation

Middle-aged women who stop smoking experience a measurable, steady decline in risk of stroke, heart disease, and death from any cause in comparison with women who continue to smoke cigarettes. This finding comes from an observational study of 117,000 nurses who were aged 30 to 55 years in 1976 and were followed through 1988. Among the women who quit smoking, risk of CHD fell by onethird during the first 2 years after cessation and thereafter decreased to that of lifetime nonsmokers over the next 10 to 14 years. Risk of stroke declined to that of nonsmokers within 2 to 4 years after quitting cigarette use, regardless of the age at which the women had started or the number of cigarettes smoked daily. Compared with lifetime nonsmokers, women who started smoking before the age of 15 were found to have slightly more than three times the risk of death from any cause during the study period, former smokers had a 29percent greater risk of dying, and women who continued to smoke had an 87-percent greater risk of dying during the study period. The results of this study confirm the benefits of smoking cessation for women, even after years of cigarette use.

### Gender Differences in Smoking Cessation and Airways Reactivity

Chronic obstructive pulmonary disease (COPD), almost all of which is smoking-related, resulted in 93,000 deaths in the United States in 1993 and is now the fourth most common cause of death. Nonspecific airways hyperresponsiveness has recently gained increased attention as a personal characteristic that interacts with cigarette smoking to cause COPD. Results from the Lung Health Study demonstrated an increased prevalence of airways hyperresponsiveness in women who had early airflow obstruction, as compared with men, that can be explained almost entirely on the basis of differences in airway caliber and geometry. These findings suggest that smoking in women may predispose the airway to hypersensitivity and thereby increase risk for the development of COPD. Additional studies are needed on the possible synergistic effects of airways reactivity, cigarette smoking, and environmental or occupational exposures in women, and on the possible mechanisms whereby a smaller airway size could contribute to an increased airways responsiveness. The results may point the way to new approaches for prevention or treatment of COPD.

Primary Pulmonary Hypertension (PPH)

PPH is a progressive, fatal disease caused by proliferative occlusion of small pulmonary arteries. It usually leads to death within 3 years of diagnosis. PPH appears as a familial disease approximately 10 percent of the time and affects women, usually of childbearing age, 2 to 3 times more frequently than men. An NHLBI-supported study is examining the pattern of PPH inheritance in a large number of families to improve understanding of the mode of inheritance and genetic features of PPH. Results of the study to date reveal that more women than men have the gene and that women with the gene are more likely than men to develop the disease. The study also reported, for the first time, that more female (57 percent) than male (43 percent) infants are born to persons carrying the gene, which suggests that the gene may result in selective loss of male fetuses or may affect the developmental process. These results support previous findings that suggest a tendency for the disease to develop in younger members of subsequent generations in affected families, a phenomenon called genetic anticipation. These features are clues to the molecular basis of familial PPH that provide direction for

the search for the responsible gene and further insight into the pathogenesis of this disease.

### Thrombocytopenias in Women and Neonates

Immune thrombocytopenia is characterized by platelet destruction due to formation of antibodies. It is a common hematologic problem with a peak incidence in the third and fourth decades, and women are more frequently affected than men, sometimes in association with the menstrual cycle or with pregnancy. Thrombocytopenia in fetuses and neonates, which can be life-threatening, results from the formation of maternal antibodies to paternal antigens expressed on the fetal platelets. Recently, significant progress has been made in understanding the biochemistry of the platelet membrane and identifying the major antigens on platelet surface glycoproteins. Immune mechanisms involved in the response of pregnant women to fetal platelet proteins are being studied. A major achievement is production of stable monoclonal antibody from patients with immune thrombocytopenia. A parallel activity is utilization of a mouse model to delineate the relative contributions of genetic factors and immune responses to development of thrombocytopenia. Finally, two major platelet domains that have been implicated in the development of thrombocytopenia have been cloned and successfully produced on a large scale in bacteria. These accomplishments provide valuable information for determining the pathogenesis, diagnosis, and treatment of immune thrombocytopenia.

#### Prevention and Translation Activities

The NHLBI Office of Prevention, Education. and Control addresses women's health issues as part of practice guidelines for physicians and as the focus of special working group reports on cardiovascular and pulmonary diseases in pregnancy. For example, National High Blood Pressure Education Program guidelines on detecting and treating hypertension address oral contraceptives, pregnancy, and HRT. NCEP practice guidelines also deal with a variety of women's issues, including use of HRT to prevent CHD in postmenopausal women. Treatment of asthma during pregnancy is the focus of a special working group report of the National Asthma Education and Prevention Program. In light of studies showing that women are inclined to delay in seeking treatment for a heart attack, the National Heart Attack Alert Program is developing a special report and educational approaches tailored to women.

NHLBI has developed a variety of education materials specifically for women. For example, a series of fact sheets about reducing CVD risk factors was developed for Native-American women, in collaboration with the Indian Health Service. In the summer of 1994. the Institute published a special issue of the HeartMemo newsletter that focused entirely on heart disease and women and provided its 22,000 readers with a compendium of information on risk factors, as well as a review of NHI BI-funded research on women. The popular Healthy Heart Handbook for Women continues to receive wide distribution through many channels; the GPO has sold more than 28,000 copies, which makes it a bestseller. In 1994, the Institute produced a series of five fact sheets based on the handbook to ensure that the information is accessible in a free. easy-to-reproduce format. A sixth fact sheet, now in production, addresses diagnosis. treatment, and other issues of concern to women who already have CHD, and a seventh will report the newly released results of the PEPI trial

#### Initiatives

#### Requests for Proposals (RFPs)

- Evaluation of Ischemic Heart Disease in Women

  The purpose of this RFP is to improve the diagnostic reliability of cardiovascular testing in evaluation of ischemic heart disease in women (RFP–NHLBI–HC–94–13).
- Angiographic Studies in Women— Coordinating Center/Clinical Centers
  The purpose of this RFP is to assess whether
  HRT and/or antioxidant treatment will
  stabilize or inhibit progression, or induce
  regression, of coronary plaques in women
  (RFP-NHLBI-HV-94-16 and RFP-NHLBIHV-94-17).

#### Request for Application (RFA)

 Effects of Sex Hormones on Coronary Artery Reactivity
 The purpose of this RFA is to study the roles of sex hormones in the physiology and pathophysiology of the coronary vasculature (RFA–NIH–93–HL–05–H).

#### NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

The National Institute of Allergy and Infectious Diseases (NIAID) has expanded its women's health efforts to address the national health challenge of disease prevention for women. NIAID supports more research than ever on women's health issues and has intensified its efforts to recruit women for clinical trials. With other institutes across NIH, NIAID has sponsored conferences and workshops, providing a forum for researchers to discuss their findings and explore ways to apply new information and technologies to advance knowledge and understanding of this field of study.

In 1994, NIAID established the Office of Research on Minority and Women's Health (ORMWH), which assists the Institute in the design and implementation of clinical trials that include minorities and women. It also facilitates collaborations between NIAID and the NIH Office of Research on Women's Health (ORWH) and other institutes on research projects involving women. In addition, ORMWH provides information to female students and researchers concerning NIH funding mechanisms and informs the scientific community and the general public about NIAID research on women's health. The ORMWH Women's Health Program Coordinator serves as a representative to the ORWH Coordinating Committee on Research on Women's Health.

NIAID conducts a considerable amount of research on women's health issues because many of the diseases within its purview inordinately affect women. For example, systemic lupus erythematosus (SLE) occurs nine times more often in women than in men. Other diseases, such as pelvic inflammatory disease, are unique to women. Certain diseases, such as acquired immunodeficiency syndrome (AIDS), are more common in men than women, but the incidence among women is increasing rapidly. Of most significance, NIAID has sponsored research on maternal-fetal transmission of disease, on topical microbicides, and on the impact and progression of the AIDS epidemic among women and their children

Of the five research areas in women's health (epidemiology, pathogenesis, diagnosis, prevention, and treatment), NIAID puts particular emphasis on prevention because an effective preventive therapy can save lives and avert suffering. Preventive therapies also have been shown to be extremely cost-effective.

#### Accomplishments

#### Etiology and Pathogenetic Mechanisms Involved in Autoimmune Diseases

In collaboration with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and ORWH, NIAID provided support for four program projects focused on increasing understanding of the etiology and pathogenetic mechanisms involved in autoimmune diseases. This program supports collaborations between basic and clinical researchers for research on the mechanisms that underlie autoimmune diseases. Two of these programs are renewals of very successful and productive programs. Several of the projects use state-of-the-art techniques including transgenic animals to address regulation of the immune response.

In collaboration with ORWH, NIAID was able to support a fifth study of the effects of silicone polymers and their breakdown products on the immune system and how these changes might contribute to the development of autoimmune diseases. This application was initially submitted in response to an RFA, "Effects of Silicone on the Immune Response."

Two ongoing studies to produce monoclonal antibodies against different regions of major histocompatibility complex (MHC) molecules, which are important in autoimmune responses, are supported by NIAID. One study uses the collagen-induced arthritis model to study the cell interactions leading the immune response. These studies may lead to new therapies for rheumatoid arthritis.

Abnormalities of the fas gene are associated with autoimmune diseases in mice and humans. Fas is a cell surface receptor belonging to the nerve growth factor receptor-tumor necrosis factor-receptor family of signalling molecules that act during the process of apoptosis (programmed cell death). A form of fas that lacks the transmembrane region and is therefore soluble, upon injection into normal mice, results in altered lymphocyte development and increased proliferation in response to self

antigens. In contrast, MRL-lpr/lpr mice develop an autoimmune, lupus-like disease, including arthritis and glomerulosclerosis. In these mice, retroviral DNA found in the fas gene causes decreased expression of the fas. By replacement of the mutated gene with a normal fas gene, researchers have prevented the development of generalized autoimmune disease in these animals. They also defined the cellular site of action of fas, by inserting a normal fas transgene, which was expressed in T cells but not B cells of these mice. It was observed that the levels of soluble fas are elevated in the serum of 60 percent of a series of patients with SLE. This increase in soluble fas found in patients with SLE, and the fact that this molecule is implicated in the MRL-lpr/lpr mouse model of lupus, suggest that fas may play a critical role in human autoimmune disease.

#### Organ Transplant

### Anti-Idiotypic Regulation of the Immune Response to HLA— The Gender Effect

Organ transplantation has reached a crisis due to an inadequate supply of organs donated for transplantation. A limited supply of organs brings into focus the question of equity in organ distribution with respect to recipient race and gender. Numerous studies demonstrate that the waiting time (for an organ) for non-white races (e.g., African American) is longer than for Caucasians. In addition, the waiting time for women of all races is longer than for their male counterparts. The major biological reason for this is, to a greater degree, that woman have been sensitized to HLA antigen (allosensitization) by pregnancies. Work conducted within the scope of this research grant has addressed the question of this allosensitization in the regulation for the immune response to organ allografts. Mechanisms were studied in allograft immunity. The results of this study showed that patients with a history of anti-HLA antibodies specific for the donor's HLA antigen can be safely transplanted if they exhibit Ab2 at the time of transplantation. In contrast, presensitized patients without Ab2 lost the graft to hyperacute or acute rejection. This has important implications for the immunogenetic evaluation of transplant candidates. Female recipients who have been sensitized to HLA antigens as a result of pregnancies can be safely transplanted if

they show specific anti-idiotypic antibodies at the time of transplantation. Testing for Ab2 improves the likelihood of finding a suitable donor for a sensitized recipient.

#### Effect of Donor- and Recipient-Gender Disparities on Fatal Graft-Versus-Host Disease in a Mouse Model for MHC-Matched, Unrelated-Donor Bone Marrow Transplantation

It has long been recognized that gender difference in humans can aggravate graft-versus-host disease (GVHD) in people receiving bone marrow transplants. The prevailing assumption, supported by a retrospective study by the International Bone Marrow Registry (supported by NIAID and NCI), was that MHC-matched marrow transplanted from a female donor into a male recipient produced the most severe GVHD. presumably because the female recognized the male H-Y antigens as foreign H-Y antigen is a minor histocompatibility antigen (mHC). However, other reports described equally severe GVHD in male-to-female transplants and gender-matched transplants (in addition to MHC) were observed to have a more favorable GVHD prognosis. These discrepancies prompted an NIAID-supported investigator to establish a properly controlled study in animals as such a study is not ethically or medically feasible in humans. He found, using an MHC-matched, unrelated donor mouse model, that in addition to GVHD reactions against male H-Y antigen, reaction against female H-X antigen is also possible

#### Pregnancy

### Suppression of B Lymphopoiesis During Normal Pregnancy

This is the first description of pregnancy-related effects on B lineage lymphocytes in the bone marrow. NIAID investigators described a highly selective depression of IL-7 responsive precursors (B cells) in the marrow and spleen. Mature B cell numbers were not affected. It has long been appreciated that there is a relationship between sex hormones and the development of the immune system, e.g., transient involution of the thymus during pregnancy was first described in 1913. Subsequent studies showed that injection of estrogen also caused atrophy of the thymus. Diminishing of B cells in marrow could somehow facilitate establishment of maternal-fetal tolerance during pregnancy. It

is well documented that autoimmune diseases, such as SLE, that are mainly dependent on polyclonal B cell activation and circulating immune complexes, are enhanced by estrogen and worsen during pregnancy. In contrast, autoimmune diseases that are dependent on T cell activation are suppressed by estrogen and improve during pregnancy. The connection between hormones and the production of new lymphocytes remains obscure. NIAID investigators have demonstrated, in mice, a marked reduction in B lymphopoiesis that occurs during pregnancy. They also show that B lymphocyte precursors are selectively depressed after a single injection of estrogen

#### Fetal Maternal Tolerance: Molecular Studies on the HLA System and Establishment of an Animal Model for Evaluation of the Immune Response During Gestation

During normal pregnancy, a semiallogeneic fetus is not rejected by the maternal immune system. The immuno-privileged status of the fetus has been the subject of considerable investigation. Since molecules encoded by the HLA gene family have a central role in the regulation of the immune response, it has been suggested that the regulation of their expression at the maternal-fetal interface is a critical aspect of gestation. A potential mechanism of protection is indicated by the fact fetal trophoblast cells, the only fetal cells that come in direct contact with the maternal tissue, have a unique pattern of HLA gene expression. To further understand the expression of human trophoblast-specific gene, HLA-G, and its regulation in vivo, HLA-G-expressing transgenic mice were established. The results of these studies demonstrated the importance of the 5-foot upstream region of HLA-G for extraembryonic expression in vivo. In particular, a distal upstream element within a 250-bp fragment located 1.1kb distal to the HLA-G translation start site is absolutely required for efficient extraembryonic expression in vivo. This transgenic mouse model should provide means by which valuable insight into the biologic function of the extraembryonic expression of HLA-G can be gained

#### Circulating Protein Present in Pregnant Women Is Associated with an Important Eosinophil Protein

A previously unrecognized association between pregnancy-associated plasma protein-A (PAPP-

A) and the proform of eosinophil major basic protein (pro MBP) has been demonstrated. PAPP-A is produced by trophoblastic tissue of the placenta and is present in large amounts in the serum during the third trimester. Coincidentally, the plasma level of an MBP of the eosinophil granule is greatly elevated during pregnancy. Immunohistochemically, MBP localizes to the x-cells and giant cells of placenta and has been purified from placental tissue. MBP isolated from the eosinophil granule is cytotoxic to mammalian cells and has been implicated in tissue damage associated with eosinophil infiltrates; however, its role in pregnancy and/or parturition remains speculative.

#### Asthma

#### Demonstration and Education Research Project Entitled Asthma Management in Inner City Patients

Studies have indicated that, regardless of race, lower socioeconomic status is a strong risk factor for asthma morbidity. This study is designed to test the hypothesis that lower socioeconomic status in asthmatic adolescents leads to higher morbidity because of limited access and utilization of health care and increased exposure to indoor aeroallergens and irritants. However, the male/female ratio changes after adolescence. After the age of 15, women compose 75 percent of hospital inpatients because of asthma. The pool of 360 adolescent asthmatics recruited for this demonstration and education research project provides an opportunity to evaluate factors related to adolescence that may differentiate women from men. The hypothesis is that adolescent girls experience higher asthma morbidity than boys as a result of two factors: greater exposure to indoor allergens and irritants and higher incidence of depression. Higher morbidity will be studied by modifying the questionnaire to capture detailed information on household chores, time spent indoors, exposure due to irritants such as smoke, and exposure to allergens. Depression will be assessed by administering the Center for Epidemiologic Studies Depression Scale screening tool to adolescents to assess whether depression is associated with increased asthma morbidity and whether females have higher scores than males.

Another study of this program is designed to test the efficacy of a multifaceted asthma

management program for adult asthmatics in East St. Louis, Illinois. Asthma prevalence is increasing in all segments of American society and particularly in African-American residents of the inner cities. Moreover, the applicant has noted that in studies, respondents from the inner city in a focus group or structured survey were largely women. Indeed, the female gender is a risk factor for asthma among African-American women. Included in this research plan is a study of factors influencing asthma self-care management decisions among African-American women.

### Impact of Hormonal Changes on Asthma in Women

Women with asthma may represent a distinctive subgroup of patients with unique factors that precipitate their disease. While previous studies have suggested that up to one-third of women with asthma report worsening of airway symptoms prior to or during their menstrual cycles, these studies have serious limitations. This research project will explore the relationship of asthma to the menstrual cycle in a selected group of asthmatic women who demonstrate symptoms and/or peak flow changes prior to the onset of menstruation and in a control group of asthmatic women. Bronchial responsiveness to methacholine will be assessed before and after menstruation, as well as the relative contributions of atopy, infection, emotional state, and hormonal and mediator changes to premenstrual exacerbations of asthma. The hypothesis suggests that increased bronchial reactivity may underlie these premenstrual symptom changes.

#### Multivalent Group B Strep (GBS) Conjugate Vaccine

In the multidisciplinary GBS contract awarded last year, significant effort will be expended on the refinement of a multivalent GBS conjugate vaccine. Studies will also be implemented to better understand the epidemiology of the disease, the basic biology of the organism, pathogenesis of the disease, and which traits are important for GBS virulence that will enable investigators to define new targets for potential preventative measures and/or therapies for the future. The vaccine constructs that are developed under this contract will be clinically evaluated in the Maternal Immunization Group at Baylor College of Medicine.

#### Human Immunodeficiency Virus (HIV)

Researching Zidovudine (ZDV) Effects on a Selected Group of HIV-Infected Pregnant Women To Reduce the Risk of Perinatal HIV Transmission by Approximately Two-Thirds

NIAID sponsors a clinical trial in collaboration with the National Institute of Child Health and Human Development (NICHD), the National Institute of Health and Medical Research (INSERM), and the National Agency of Research on AIDS (ANRS) of France researching zidovudine (ZDV) to study the effects on a selected group of HIV-infected pregnant women to reduce the risk of perinatal HIV transmission by approximately two-thirds.

Maternal-Fetal Transmission of HIV NIAID-sponsored investigators on 10 or more projects are investigating the maternal-fetal transmission of HIV in a variety of studies.

#### Women in CPCRA Trials

Similarly, NIAID sponsored HIV clinical trials, including but not limited to the women in CPCRA trials, to investigate the risk of death, disease progression, and mortality of 768 women and 3,779 men enrolled in 11 CPCRA protocols.

AIDS Clinical Trial Group (ACTG) 076 Results from ACTG Protocol 076, a clinical trial sponsored in collaboration with NICHD. INSERM, and ANRS, indicate that ZDV administered to a selected group of HIVinfected pregnant women (those with CD4+ lymphocyte counts ≥200 cells/&L and limited or no prior anti-retroviral therapy) and their infants can reduce the risk of perinatal HIV transmission by approximately two-thirds. The use of ZDV in this manner has the potential to significantly reduce the rate of motherto-child transmission, which in turn would have a major effect on child mortality. However, the results of this study are directly applicable only to HIV-infected women with characteristics similar to women who entered the study, and long-term risks of ZDV used in this manner are not known.

Maternal-Fetal Transmission Reduced From 25.5 to 8.3 Percent in Infected Women Treated with Azidothymidine (AZT) During Pregnancy ACTG 076, a randomized, double-blind, placebo-controlled trial evaluated the efficacy, safety, and tolerance of AZT for reducing the risk of transmission of HIV from HIV-infected pregnant women to their infants. The study was conducted at 59 sites of the ACTG Eligible patients were HIV-infected pregnant women (14 and 34 weeks gestation) who had no anti-retroviral therapy during the current pregnancy, had CD4 lymphocyte counts >200 cell/mm3, and had no clinical indications for antepartum ZDV. Women were stratified according to gestation age (14 to 26 weeks; > 26 weeks) and randomized to receive either ZDV or placebo. The ZDV regimen consisted of antepartum zidovudine (100 mg five times a day), intrapartum ZDV (2 mg/kg iv over I hour, then Img/kg until delivery), and newborn ZDV (2 mg/kg orally every 6 hours for 6 weeks) At the time of the first interim efficacy analysis, 477 women had been enrolled with sufficient information regarding outcome for 363 births, 180 in the ZDV group and 183 in the placebo group. Of the 53 infants infected with HIV, 40 were on placebo, and 13 were on ZDV. The transmission rate in the placebo arm was 25.5 percent, while the transmission rate in the ZDV arm was 8.3 percent. The treatment was well tolerated among women and infants.

### HIV-1 Is Transmitted From Mother to Child in Utero

Although there is evidence of maternal-fetal HIV transmission in utero, intrapartum, and postpartum, the exact timing and relative frequency of each are poorly defined. Also unknown are the effects of maternal viral factors (tropism/phenotype) on transmission risk and the effects of the time of transmission and transmitted virus phenotype on the onset of symptoms in infected infants. NIAIDsupported investigators prospectively followed 96 HIV-infected pregnant women and their infants. Of the 74 pairs with known infantinfection status, 22 of the 74 mothers (28 percent) transmitted the virus. Eleven of the 22 infants (50 percent) were assumed to be infected in utero (positive culture at birth), and the remainder were infected intrapartum (negative birth/neonatal cultures with subsequent positive cultures).

Inoculation of Amniotic Fluid in Pregnant Monkeys Produces a High Incidence of Infection with Simian Immunodeficiency Virus (SIV)

The mechanisms of transmission of HIV from infected mothers to their newborn infants are

not fully understood. An NIAID-funded investigator has developed a reliable and reproducible model for studying transmission in primates infected with SIV, a virus closely related to HIV. Using ultrasound guidance, the investigator inoculated the amniotic fluid of pregnant rhesus monkeys with SIV. Seven of eight females exposed by this method became infected with SIV, and six of seven infants born to infected mothers were born with the SIV infection. The fact that one SIV-infected mother gave birth to a noninfected infant suggests that contact with infected amniotic fluid may not in itself be sufficient for virus transmission.

#### Adherence of Lymphocytes and Mononuclear Cells to Microvilli of the Placenta May Be Important in Explaining Virus Transmission Across the Placenta

A Division of Acquired Immunodeficiency Syndrome (DAIDS) grantee has made progress toward understanding placental transmission of HIV. An NIAID grantee has characterized the adherence of a human lymphocytic cell line and normal human peripheral blood mononuclear cells (PBMCs) to primary cultures of term human syncytiotrophoblast (the outer layer of trophoblast). Scanning electron microscopy revealed that lymphocytes and PBMCs adhered to free microvillous surfaces of the syncytiotrophoblast masses. This finding raises the possibility that cell-to-cell spread of the virus may be an important phenomenon in vivo and may explain how infected cells or the virus cross the placenta.

## Gender Differences Are Apparent in Susceptibility to the Toxic Effects of Antiparasitic Drugs

Recent work conducted by a DAIDS contractor has shown that female animals were more sensitive to the toxic effects of the antiparasitic drug pyrimethamine (PYR) than were male animals. The female group exhibited more deaths and died earlier in the study than males. Decreases in both red and white blood-cell counts were seen in females, but not in males. A major gender-related difference was also seen in the effect of cell-mediated lysis, where decreases were seen only in females. Similar genderrelated differences were also observed when PYR was administered at the same time as AZT. These results suggest the importance of studying drug toxicity and potential interactions for effects in both males and females

and being alert for differences in response between the two genders.

#### The Probability of HIV-1 Transmission From a Pregnant Woman to Her Baby Increases with the Level of Infectious HIV-1 in Her Blood

An NIAID-funded investigator examined the relationship between maternal HIV-1 titer and the occurrence of mother-to-child transmission. Nineteen mother-child pairs were studied: in five pairs, HIV-1 transmission occurred. The mother's viral titer was measured by endpoint dilution culture of PBMCs. Mother-to-child transmission occurred in four of six (67 percent) women with viral titers greater than 125 infectious HIV per million cells and only in one of 13 (7.6 percent) women with lower viral titers. These results suggest that the HIV titer in pregnant women may be used to identify those women who are at high risk of transmitting HIV to their infants, and these women may benefit from therapeutic strategies designed to decrease transmission by lowering the viral load.

#### Placental Cells Are Similar to Other Cell Types in Their Metabolism of AZT

The ability of cells in the placenta to metabolize AZT has been established and quantitated by NIAID-funded investigators at the University of Washington. They used human trophoblast and Hofbauer cells (macrophages in the chorionic villi) maintained in cell culture and discovered that both cell types metabolize AZT similarly to other cell types, with formation of diphosphate as the rate-limiting step and AZT triphosphate as the active metabolite. Thus, it is likely that the placenta maintains intracellular levels of AZT and its metabolites that are comparable to those maintained in the general circulation, and they may act to inhibit transmission of HIV from mother to infant.

### Maternal Vitamin A Deficiency and HIV Transmission

Researchers in Malawi have shown an association between maternal vitamin A deficiency and a threefold to fourfold increased risk of mother-to-child transmission of HIV. Following a cohort of 338 HIV-positive pregnant women through antenatal clinics and delivery, the DAIDS-supported research team determined that 21 percent of mothers transmitted HIV to their infants. Where transmission occurred; mothers had a significantly lower mean level

of serum vitamin A than in pregnancies where transmission did not occur. The biological mechanisms underlying this relationship are unknown, but it is hypothesized that they may include the role of vitamin A in immunity and maintenance of mucosal surfaces.

#### Women in CPCRA Trials Are at Increased Risk of Death, but Not Disease Progression, as Compared to Men

Disease progression and mortality were compared between 768 women and 3,779 men enrolled in 11 CPCRA protocols. The median CD4+ cell count at enrollment into the cohort was 240 cells/mm3 for women and 137 cells/ mm<sup>3</sup> for men. Outcome measures examined were survival and opportunistic events. Women were younger (36 versus 38 years of age), more likely to be African-American or Latino/Hispanic (78 percent versus 44 percent), and more likely to have a reported history of injectable drug use (49 percent versus 27 percent). Women were at increased risk of death. The adjusted relative risk for death was 1.33 and for disease progression was .97. Women were also at increased risk for bacterial pneumonia and at reduced risk for the development of Kaposi's sarcoma (KS) and oral hairy leukoplakia. Among patients without a history of disease progression at entry, death was the first event reported for more women than men (27.5 percent versus 12.2 percent). Treatment differences between men and women were significant for PCP prophylaxis; women were significantly less likely than men to be on PCP prophylaxis. These findings may reflect a differential access to health care and/or socioeconomic status and social support for women compared to men.

#### Several Other NIAID-Sponsored Protocols Addressing Women-Specific Issues Are Underway, Including the Following:

#### CPCRA 010

A Randomized Trial Comparing Fluconazole and Placebo for Primary and Secondary Prophylaxis of Mucosal Candidiasis in HIV-Infected Women (closed).

#### ACTG 200

A Randomized Trial of Topical Vaginal 5-Fluorouracil (5-FU) Maintenance Therapy versus No Further Therapy After Standard Treatment for High-Grade Cervical Dysplasia in HIV-Infected Women (open).

#### DATRI 005

A Study To Evaluate the Sensitivity of Laboratory Methods for Measuring the Amount of HIV in Vaginocervical Secretions (methodology study—no patients will be accrued).

#### ACTG 233

A Phase I Study of Biocine/Chiron HIV Vaccine in HIV-Infected Pregnant Women (open).

#### AVEG 102/ACTG 234

A Phase I Study of MicroGeneSys HIV Vaccine in HIV-Infected Pregnant Women (open).

#### AVEG104/ACTG 235

A Phase I Study of Genentech HIV Vaccine in HIV-Infected Pregnant Women (open)

#### ACTG 185

A Phase III Randomized, Double-Blind Controlled Study of the Use of HIVIG for the Prevention of Maternal-Fetal HIV Transmission in Pregnant Women Receiving Zidovudine (open).

#### ACTG 249

A Phase I Trial To Evaluate Didanosine in HIV-Infected Pregnant Women (in development).

#### ACTG 250

A Phase I Study of the Safety and Pharmacokinetics of Nevirapine in Pregnant Women and Neonates (open).

#### ACTG 293

A Randomized Trial of Oral Isotretinoin versus Placebo for Low Grade Cervical Dysplasia in HIV-Infected Women (in development).

#### ACTG 875

A Gynecological Substudy of ACTG 175 and ACTG 196. This study is designed to incorporate gynecologic data collection into ACTG clinical trials, improve enrollment, assess the effects of therapy on gynecologic conditions, and study endpoints specific to women (open).

### The Women and Infants Transmission Study (WITS I/II)

WITS is a collaborative, multi-center study in five locations: Chicago, Boston, Puerto Rico, New York City, and Houston. Although the major component of this study is to research HIV transmission during pregnancy or birth, WITS II researchers also examine factors related to HIV progression in women during pregnancy.

Recent data from the WITS suggest that the length of membrane rupture (ROM) during labor appears significantly related to risk of perinatal HIV transmission. Among women with less than 4 hours of ROM, 12 percent of infants were infected; among those women with 5 to 23 hours of ROM, about 22 percent of infants were infected; and among women with ROM greater than 24 hours, 50 percent of infants were infected (p< 0.001). This finding may have important implications for management of labor and delivery for HIV-infected pregnant women.

#### The Women's Interagency HIV Study (WIHS)

Enrollment for the study began in September 1994. The five study sites, located in New York, San Francisco, Los Angeles, Washington, DC, and Chicago, will study immunologic assessments and the characterization of the manifestations of HIV disease in women. A smaller group of non-HIV-infected women will provide comparative immunologic and clinical data.

### • The Preparation for AIDS/HIV Vaccine Evaluation (PAVE)

PAVE supports studies of HIV sero-incidence in domestic and international cohorts and other research to determine the feasibility of conducting HIV vaccine trials in populations of highest risk. Most PAHO/NIAID and PAVE studies include women.

### • The Cohort Study of Pregnant Women Who Have Seroconverted

As part of PAVE, a cohort study of 687 pregnant women in Malawi showed that 43 enrollees had seroconverted within the first 2 years of enrollment. Seroconversion rates by semester were 1.4 percent, 1.7 percent, 2.4 percent, and 4.3 percent, respectively.

#### The Phase I/II Safety and Toxicity Study of HIVIG

Two other international studies were initiated in Fiscal Year 1994. The first, a Phase I/II safety and toxicity study of HIVIG in a perinatal clinic in Uganda, will examine 400 mother-infant pairs.

#### The Properties of Breast Milk That Are Relevant to Transmission Among HIV-Infected Pregnant Women The second study evaluates the properties of breast milk that are relevant to trans-

of breast milk that are relevant to transmission among HIV-infected pregnant women in Haiti.

#### The Phase I/II Safety and Toxicity Study of Fogarty HIVIG

Initiation of a Phase I/II safety and toxicity study of HIVIG was done in a perinatal clinic in Uganda. This study includes production of the HIVIG product using Ugandan donors. A 400 mother-infant pair efficacy study will follow.

#### Sexually Transmitted Diseases (STDs)

### Community-Based Intervention of STD Treatment

NIAID is funding a community-based intervention of STD treatment as an approach to preventing HIV infection in Uganda. Based on extensive behavioral research to identify sexual networks between villages, randomization of villages was based on clusters of interactive villages, thereby avoiding contamination of communities. Both STD and HIV outcomes are being measured.

#### **Topical Microbicide**

Applications for program projects in topical microbicides have been reviewed, and a funding plan is being developed. NIAID will make these awards early in 1995.

### Applications for the STD Cooperative Research Center

These applications have been received and will be reviewed in the spring and awarded in July 1995.

#### A Human Papillomavirus (HPV) DNA-Sequence Database

NIAID has established this database. The first volume of the compendium was published in Fall 1994.

#### Community-Based Trials To Prevent Blinding Trachoma

These trials to prevent trachoma caused by chlamydial infection are in progress. Single-dose therapy is being compared to daily treatment with eye ointment.

### The Phase 1 Evaluation of NIH's Research Program on Condoms

This evaluation was completed. Plans for Phase 2 are in progress.

### Additional Clinical Studies of Existing Spermicides

NIAID will sponsor these clinical studies to determine safety and efficacy with respect to prevention of STDs and HIV infection

#### A Patient Registry for Children with Recurrent Laryngeal Papillomatosis

NIAID will collaborate with the Centers for Disease Control and Prevention (CDC) to establish a registry for this disease, an adverse outcome of pregnancy related to HPV infection

### The Phase 2 Evaluation of NIH's Condom Research

NIAID will participate in this evaluation

A Monograph on Adolescents and STDs This document is being planned. It will be multidisciplinary in scope, including biomedical, behavioral, and clinical aspects of our current state of knowledge and future directions.

#### Chronic Fatigue Syndrome (CFS)

# Updating the CFS Case Definition NIAID researchers were active collaborators with CDC and other CFS researchers and physicians in the CDC effort to revise and update the CFS case definition.

#### First Phase I Safety and Immunogenicity Trials of Types Ia and Ib GBS Conjugate Vaccines

These trials were conducted in nonpregnant women at Baylor College of Medicine. The vaccines were found to be safe and considerably more immunogenic than the polysaccharide vaccines. Two Phase II trials of the type III GBS conjugate vaccine are underway.

Continued Research on the Causes of CFS NIAID will continue to support research on a broad front directed at understanding the underlying causes of CFS and to be responsive to opportunities suggested by new findings. The newly established NIAID Cooperative

Research Centers provide a mechanism for expediting funding of pilot studies.

#### Initiatives

#### Requests for Proposals (RFPs)

· Mechanisms of Embryonic/Fetal-Maternal Tolerance NIAID, together with NICHD and ORWH, issued a request for application (RFA) for Fiscal Year 1995 entitled "The Mechanisms of Embryonic/Fetal-Maternal Tolerance." This RFA invites applications for basic studies designed to identify the underlying immunologic and/or genetic mechanism(s) that protect the embryo and fetus from maternal rejection and to elucidate the interactions of the fetal and maternal immune systems in successful pregnancy. The goal of this initiative is to promote research that will advance our understanding of the underlying mechanisms of

 Development of Techniques and Research into the Isolation and Characterization of MHC-Bound Self-Peptides Linked to the Pathogenesis of Autoimmune Diseases

this unique form of immunologic tolerance

and lead to improved clinical applications.

NIAID funded three contracts out of eight proposals received in response to an RFP. These groups will investigate the target peptides in a variety of autoimmune diseases, including insulin-dependent diabetes mellitus, systemic lupus erythematosus, multiple sclerosis, and ankylosing spondylitis. In addition, peptides in several animal models of autoimmune disease will be investigated.

• STD Diagnostics Initiative

This RFP is a small grants program estalished in collaboration with WHO/GPA. Applications are planned for review in early 1995. NIAID will co-sponsor these awards.

#### Requests for Applications (RFAs)

Asthma, Allergic, and Immunologic
Diseases Cooperative Research Centers
NIAID issued an RFA in Fiscal Year 1994 in
order to increase knowledge of the etiology
and pathogenetic mechanisms of immunologic diseases and to apply an expanded
knowledge base to the development of

improved methods of diagnosis, treatment, and prevention of immunologic diseases, including autoimmune diseases.

Studies of the Structure and Function of the Eosinophil Granule Proteins This is an RFA to study the eosinophil granule proteins, including the major basic protein (MBP) and others, that are being purified from eosinophil granules to test the ability of these proteins to induce adhesion molecules on bronchial epithelium. The structure of MBP will also be studied. It has been found that MBP is elevated in the sera of pregnant women. Previous work by the applicant indicated that although MBP levels did rise in a majority of women just prior to the onset of labor, about 20 percent of women showed no such rise, and even in those women where the MBP levels did rise. it was not possible to predict the onset of labor. The hypothesis is that 14kDa MBP is derived by cleaving proMBP during the latter stages of pregnancy and causes labor, either directly or by increasing uterinesmooth-muscle responsiveness to mediators such as prostaglandins. Premature labor is a major determinant of low birthweight and thus neonatal mortality and morbidity. The use of the serum 14kDa MBP marker could help to identify individuals who need treatment for preterm labor.

#### Interdisciplinary Programs in Autoimmunity

NIAID was recently joined by the Juvenile Diabetes Foundation International and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in issuing an RFA to investigate the basic, molecular, immunologic, and genetic mechanisms in the pathogenesis of autoimmune disease and the development of innovative therapies for these diseases.

#### Mechanisms Underlying Immunotherapy Trials in Autoimmunity

This is an NIAID RFA whose studies would expand the clinical evaluation of these experimental treatments by incorporating basic research on the molecular and immunologic mechanisms underlying these immune therapies. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIDDK, and ORWH joined in support of this RFA.

#### An RFA To Renew the STD Cooperative Research Centers

This RFP was advertised. As a reflection of the success of the behavioral research projects, inclusion of a behavioral or epidemiological project was required.

#### • An RFA To Establish STD Diagnostic Development Groups

This RFA is being advertised, and awards will be made in Fall 1995.

 Chronic Fatigue Syndrome Cooperative Research Centers (CFSCRC)
 In 1994, NIAID issued an RFA for CFSCRC.

#### Program Announcements (PA)

- NIAID issued a PA in collaboration with NIDDK, "Autoimmune Endocrine Disease." This was done in order to stimulate investigators to study the pathogenesis, immunogenetics, and immunotherapy of these autoimmune diseases. NIAID has funded at least one new application received in response to this PA.
- NIAID continued a PA, "Cytokines in Autoimmunity," for research to promote basic research on the involvement of cytokines in the etiology and pathogenesis of autoimmune diseases and their use as modulators of disease initiation and activity.
- In response to a PA on behavioral research, four new grants have been funded. These include studies on perceived risk for STDs on adolescent development and STD acquisition in young girls on development of a social-behavioral model of STD acquisition among men, and on behavioral aspects of STD transmission in street youths.
- NIAID, NIAMS, and the National Institute
  of Mental Health (NIMH) issued a PA, "New
  Insights into Chronic Fatigue Syndrome."
  The goal of this PA is to encourage studies
  to test biologically rational hypotheses
  concerning etiology, natural history, or
  pathogenesis that will provide a better
  understanding of the syndrome leading
  to improved diagnosis and intervention.
- A monograph on STDs and adverse outcomes of pregnancy previously studied will be published in 1995.

#### Workshops/Conferences

- NIAID held workshops on several important research areas in 1994, including:
  - Adolescents and STDs, April 1994 (Rockefeller Foundation, co-sponsor);
  - STDs and Adverse Outcomes of Pregnancy, June 1994 (Centers for Disease Control and Prevention, co-sponsor);
  - STD Vaccine Development: Chlamydial Vaccines, September 1994;
  - STD Vaccine Acceptance and Compliance, December 1994; and
  - Pelvic Inflammatory Disease, December 1994.
- An NIAID workshop, Clinical Management of Chronic Fatigue Syndrome, co-sponsored by NIMH and ORWH, took place in November 1993.
- In August 1994, the Third Annual CFSCRC meeting was organized by NIAID as a discussion group among NIAID-supported researchers of chronic fatigue syndrome (CFS) who are currently investigating either cytokine or cell markers.
- NIAID will continue to sponsor CFS workshops and support conferences to advance the field. NIAID staff is in the process of consulting with the U.S. Public Health Service staff, extramural investigators, and constituency groups about the issues related to outcome measurements for CFS treatment modalities. After assimilating the comments from these groups, the staff will organize a meeting on this topic.
- On June 6 and 7, 1994, the Public Health Service held a workshop, Use of ZDV To Prevent Perinatal HIV Transmission (ACTG 076): Workshop on Implications for Treatment, Counseling, and HIV Testing, with representatives from the medical, scientific, public health, legal, and HIVinfected communities and from interested professional, community, and advocacy organizations. The workshop addressed two issues related to the results of ACTG 076: (1) treatment recommendations for the use of ZDV to reduce HIV transmission from an

infected woman to her child and (2) implications of the trial results for counseling and HIV testing.

#### NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports and stimulates research on a broad range of diseases and long-lasting, disabling conditions in the areas of rheumatic diseases, bone and mineral metabolism, orthopaedics, muscle biology, and skin diseases. The Institute supports research projects and programs, research training, and career development; collects data on the incidence and prevalence of diseases that are under study; and disseminates research findings to health professionals and the general public.

Significant gaps in knowledge currently exist both with respect to women's health issues and gender differences in diseases that affect both sexes. NIAMS supports research in the following diseases more prevalent in women, osteoporosis, systemic lupus erythematosus, rheumatoid arthritis, fibromyalgia, scleroderma, and Sjögren's syndrome.

#### Accomplishments

#### Osteoporosis

Osteoporosis is a major health problem for postmenopausal women in the United States, affecting approximately 26 million Americans. This disorder is responsible for 1.3 million fractures each year at a cost of \$7 to \$10 billion. Osteoporosis is a condition in which the bone mass is reduced, leading to thin bones that are susceptible to fracture. The major sites of fracture include the hip, wrist, and vertebra.

Women are four times as likely as men to develop osteoporosis. This is attributed to two factors: (1) women start off with a lower adult peak bone mass, and (2) women have an accelerated loss of bone following menopause. Other risk factors include early menopause; a thin, small-framed body; low calcium intake; and a lack of physical activity.

The problem of osteoporosis is likely to increase as the number of elderly people grows. The lifetime risk of hip fractures in white women is as great as the risk of breast, endometrial, and ovarian cancer combined. Hip

fracture is the most serious consequence of osteoporosis. In 12 to 20 percent of cases of hip fracture, the patient dies within 6 months. One-half of the survivors are unable to walk unassisted, and 25 percent are confined to nursing homes for long-term care. More than 90 percent of hip fractures are the result of falls. Because of this and the fact that hip fracture incidence rates rise exponentially with age, the annual number of fractures could double or triple by the year 2050.

#### Genetic Marker for Osteoporosis

Bone density is highly correlated with the risk of bone fracture. The association is stronger and more predictive than serum cholesterol is for the risk of heart attacks. About 70 percent of bone mineral density is determined by heritable factors. Recently, investigators supported by NIAMS reported an association of bone mineral density with different variants of the vitamin D receptor (VDR) gene, which may indicate that this gene plays a dominant role in the heritable component of bone density. This finding offers the potential to choose specific therapy based on genetic makeup.

#### Some Promising Results for Fluoride

Fluoride has been known for many years to have the potential for promoting the new bone formation in the adult skeleton. However, early studies of individuals taking fluoride showed that although their bone mass increased, the fractures continued at the same rate. One reason may have been the dose and particular form of fluoride used in these older studies. Recent results with a slow-release form of fluoride combined with high dietary calcium intake show a prevention effect on fractures in postmenopausal women. While several new and emerging therapies for osteoporosis appear to arrest bone loss, the goal for treating advanced osteoporosis is new bone formation. New approaches to the use of fluoride, both alone and in combination with other agents, suggest the exciting possibility of actually restoring lost bone.

#### Who Has Osteoporosis?

Osteoporosis is not symptomatic until a fracture occurs. Spine fractures are often accompanied by pain and ultimately loss of height; however, such fractures may also be unnoticed when they occur. Fracture risk is associated with bone mineral density. Although noninvasive methods for measuring bone density have existed for many years, dual energy x-ray

absorptiometry (DEXA) used in large national samples over the last 5 years is making it possible to develop population-based osteoporosis prevalence data. Based on a recent World Health Organization quantitative definition of osteoporosis that relates an individual's bone density to that of a young adult, about 15 percent of women between 50 to 59 years of age have osteoporosis, whereas 70 percent of women over 80 years of age have this condition. Overall this analysis would suggest that about 26 million women are at risk of fracture due to lower-than-normal bone mass. This information from the Rochester Epidemiology Project will soon be corroborated by the data from the National Health and Nutrition Examination Survey (NHANES), a true national sample.

### Estrogen Replacement Therapy and Fractures in Older Women

Estrogen replacement has become an accepted preventive strategy for osteoporosis in postmenopausal women. Several epidemiologic studies have shown a statistically significant reduction in hip, wrist, and spine fractures among women taking estrogen. The effectiveness of estrogen in preventing fractures in elderly women was uncertain. Recently, information on the bone density, fracture incidence, and estrogen use in 9,700 women over the age of 65 enrolled in the Study of Osteoporotic Fractures was assessed and reported. Women who currently took either estrogen or estrogen plus progestin and who started using hormone replacement within 5 years of menopause had the lowest rate of fracture. All fracture sites were affected. However, the results also indicated that this protection persisted only when estrogen continued. Previous intake of estrogen, even for as long as 10 years, failed to provide adequate fracture protection in elderly women. These results suggest that estrogen replacement therapy should be initiated early in menopause and continued indefinitely to offer optimal prevention of osteoporosis. Further studies are needed to determine the overall risks and benefits of such a regimen.

#### Osteoclast Biology

Osteoclasts, the cells that break down bone, are important components of the regulatory system that controls bone mass and determines fracture risk. These cells are important targets for many therapeutic interventions. However, it is difficult to test promising agents directly on

the cells because they are difficult to isolate and characterize. Recently, progress has been made in developing immortalized osteoclasts that could serve as important models for the testing of therapeutic strategies in osteoporosis, Paget's disease, and osteopetrosis.

### Bone Marrow, Cytokines, and Bone Remodeling

Evidence has been accumulating for some time indicating that regulation of bone and regulation of the immune system operate on common principles and employ common effectors. Osteoclasts and osteoblasts arise in the bone marrow, and their growth and activity is affected by marrow-derived cytokines. Many cytokines strongly affect bone remodeling. Sex steroids regulate the production of the cytokines, Interluekin-1. -6. and -11. In the estrogendeficient state, the secretion of these factors in the marrow is increased, and the production of osteoclastic cells rises, as does bone resorption. Animal and cell culture models support the emerging hypothesis that the mismatch between the formation and resorption of bone in both postmenopausal and age-related osteoporosis is mediated at least in part by the activity of products of the immune system, the cytokines. Basic research enhancing our understanding of the immune system is important for understanding bone metabolism and its control as well.

#### Systemic Lupus Erythematosus (Lupus, SLE)

Lupus is an inflammatory, autoimmune disease characterized by excessive production of antibodies directed against the body's own tissues. As with several of the other rheumatic diseases, lupus affects women more than men. Women are nine times more likely than men to be affected by lupus. Most commonly, women are 20 to 40 years of age when the symptoms first appear. Lupus is three times more common among African-American women than among white women. It is conservatively estimated that there are about 130,000 patients with lupus in the United States. Improved methods of diagnosis are uncovering more patients with a milder form of the disease.

In lupus, autoimmune antibodies have been shown to damage kidneys and other organs; attack brain cells, causing convulsions and psychosis; and lead to phenomena that cause clots in the lung, and also stroke. If one or more maternal antibodies cross the placenta,

heart and skin defects can result in newborn infants: also spontaneous abortions can occur This is known as neonatal lupus Lupus, therefore, has a spectrum of clinical manifestations. The course of the disease is highly variable. and the patient can be in remission and then suddenly go into a crisis. Research advances have improved considerably the outlook for people with lupus. Just 30 years ago, half of all lupus patients died within 4 years of diagnosis. Today, 95 percent of patients are alive 10 years after the disease is detected. This remarkable advancement can be attributed to improved techniques for diagnosing the disease before significant damage to the organs has occurred and to improved drug therapy

#### Gene Replacement Prevents Lupus-Like Autoimmune Disease in Mice

Researchers have found that replacing a single defective gene can correct a lupus-like autoimmune disease in mice. The gene, called *lpi* or *Jas*, plays a key role in a process known as programmed cell death or apoptosis. Apoptosis enables the body to eliminate unnecessary, damaged, or potentially harmful cells. In the immune system, apoptosis is responsible for eliminating white blood cells with the potential to attack the body's own tissues.

Normally, the immune system detects these "self-reactive" cells, and they are destroyed by apoptosis before they can do any harm. If apoptosis is defective, self-reactive cells will survive and may cause autoimmune diseases such as lupus. MRL-lpr/lpr mice spontaneously develop lupus-like diseases. These mice have a defect in the fas (lpr) gene that leads to drastically reduced production of the Fas apoptosis protein. When the defective fas gene is replaced with a normal fas gene, the mice no longer develop signs of disease. The researchers genetically engineered the mice to correct the defect in fas production in white blood cells called T cells. In these fas transgenic mice, the lupus-like disease seen in the MRL-lpr/lpr mutant mice was eliminated, and autoantibody levels were reduced.

### Rabbit Model for Lupus Produced by Immunization

Immunity against a single peptide structure may initiate an expanded autoimmune response against the molecule from which the peptide was derived. Autoantibodies from many patients with lupus bind the Sm autoantigen Recent

investigators found that rabbits immunized with two octapeptides derived from the Sm antigen develop such an expanded autoimmune response. They produce antibodies that not only bind the immunizing agents but also subsequently bind other peptides in Sm. In addition, the rabbits also develop features typical of lupus, such as proteinuria, seizures, thrombocytopenia, and anti-double-stranded DNA antibodies.

This new rabbit model describes for the first time a successful approach to antigen-induced lupus in vivo. The model suggests that the auto-immune responses in SLE progress from one or few structures to a complicated series of specificities that include the development of pathogenic antibodies. This model provides a well-defined system to study the initiating events and the immune dysregulation in lupus. Further, it may pinpoint specific antigen target structures that could be used to induce tolerance or halt the development of pathogenic autoantibodies.

#### Rheumatoid Arthritis

Rheumatoid arthritis (RA) occurs in about 1 percent of the population, more than 2 million people in the United States, affecting women about three times more often than men. While the disease can occur at any age, the peak incidence in women is between the ages of 40 to 60 years. RA is a chronic, systemic, inflammatory disorder of unknown origin, characterized largely by the manner in which it involves joints. Commonly, the small joints of the hands and feet are affected. The primary target of this crippling disorder is the joint lining (synovium), which becomes inflamed, painful, and swollen. If RA is not controlled, joint cartilage, tendons, bones, and other surrounding structures are damaged. The clinical course is highly variable. In some, manifestations are mild; in others, the disease rapidly progresses to severe disability. At present, the disease is only managed; no curative treatment is available. Patients benefit by using medical, rehabilitative, and surgical services.

#### Role of Angiogenesis in RA

Angiogenesis, the formation of new blood vessels, is a key pathologic process involved in the development of tumors and other proliferative lesions. Microscopic examination of synovial tissue biopsies from patients with RA show a striking proliferation of blood vessels. These

proliferative lesions are an essential requirement for subsequent joint destruction. Researchers have new evidence that angiogenesis may play a key role in proliferation of the synovium characteristic of RA.

Using an experimental model of arthritis in rats, researchers have found that agents inhibiting blood vessel formation prevent the onset of disease and reverse clinical and radiographic manifestations of arthritis. The agents tested are AGM-1470, a synthetic derivative of fumagillin, a product of Aspergillus fumigatus that shows a tumor inhibitory effect in animal models, and taxol, a diterpene originally derived from the inner bark of the yew tree, which is now available in a synthetic form. Treatment with AGM-1470 prevented arthritis in a rat model and reduced severity in rats with established arthritis. When combined with taxol, AGM-1470 induced significant reversal of arthritis in all experimental animals treated. The results from the experimental system strongly suggest that angiogenesis inhibitors may be a new and promising therapy for patients with RA.

### Role of Nitric Oxide in the Inflammation of RA

Nitric oxide, important in promoting smooth muscle relaxation, has also been found to mediate inflammation in arthritis. A mouse model of arthritis was found to overproduce nitric oxide. When the production of nitric oxide was blocked, arthritis failed to develop. The relevance of this finding is being examined in clinical studies of patients with RA. These studies are also relevant to the arthritis and nephritis that accompany lupus.

#### Minocycline

Results of a 48-week, multi-center clinical study of 219 adults with RA show that the drug minocycline reduces joint pain and swelling and is safe in patients with mild to moderate disease. This study was funded as a contract by NIAMS and was carried out at six clinical centers.

#### Role of Infection in Arthritis

In a novel study on the causes of some forms of arthritis, researchers have shown in animals that both a bacterial trigger and genetic susceptibility are necessary for the disease to occur. This discovery is the fruit of a research effort that began with a study to determine if a human gene called HLA-B27 was the major cause of a group of rheumatic disorders called spondylo-

arthropathies. Earlier studies showed that rats carrying the human HLA-B27 gene develop joint inflammation (arthritis) and other symptoms characteristic of the human spondyloarthropathies. Researchers now report that when these B27 transgenic rats are raised in a germfree environment, they no longer develop arthritis. This research focuses interest in determining how infection and genetic background interact to make some persons more susceptible to developing arthritis.

#### Fibromyalgia

Fibromyalgia is a disorder characterized by widespread pain and multiple, characteristic tender points. Fibromyalgia is associated with sleep disturbances, particularly nonrestorative sleep, morning stiffness, aggravation by lower temperatures, and amelioration by exercise. The precise frequency and natural history of fibromyalgia are unknown, but the disorder may affect about 2 to 3 percent of the population of the United States, and the majority of affected individuals are women. Fibromyalgia tends to overlap with a number of disorders. including irritable bowel and bladder syndromes. frequent headaches, and chronic fatigue syndrome. In 1990, the American College of Rheumatology published classification criteria for fibromvalgia. These criteria provide a uniform basis for classifying the cases and will be invaluable in conducting research in this area

New Research Initiated in Fibromyalgia In 1994, a major effort was made by NIAMS to promote research in fibromyalgia. New research grants were awarded to investigators at five major medical centers to increase understanding of the causes of fibromyalgia in order to improve diagnosis and treatment.

At Brigham and Women's Hospital in Boston, researchers will focus on the regulation of the adrenal gland in fibromyalgia. Cortisol production in normal individuals and in those with fibromyalgia, both under restful conditions and under stress, will be examined. In addition, the researchers plan to compare the mechanisms promoting cortisol production in each group. These studies will establish whether patients with fibromyalgia have a defect in adrenal hormone production that can be modified with appropriate therapy.

In a related study at the University of Michigan Medical Center, the function of the hypothalamic-pituitary-adrenal (HPA) axis will be studied in patients with fibromyalgia. For many patients, significant physical or emotional stress is often associated with the onset or worsening of disease. Researchers will test the hypothesis that the HPA axis may be functioning with a reduced response in patients with fibromyalgia and chronic fatigue syndrome.

Researchers at the University of Alabama at Birmingham will concentrate on how altered activity of specific brain structures may be involved in the painful symptoms of fibromyalgia. The investigators will measure brain activity related to perception and thresholds for pain, transmission of pain signals, and psychological distress, including anxiety and depression.

At Vanderbilt University School of Medicine, researchers will use magnetic resonance imaging and magnetic resonance spectroscopy techniques to study patients with fibromyalgia. The goal of these evaluations is to document that current treatments, such as amitriptyline or physical therapy, do in fact improve the ability of the muscle to perform sustained exercise

The causes of a post-Lyme disease syndrome as a model for fibromyalgia will be studied at the New York Medical College in Valhalla. Lyme disease is an infection caused by a tick-borne bacterium. Some patients develop a fibromyalgia-like condition following Lyme disease. Patients with this form of post-Lyme syndrome often complain of widespread muscle and joint pains, fatigue, and difficulty with memory and concentration. These symptoms often persist despite antibiotic therapy to treat the Lyme disease infection. Investigators will examine and conduct various tests on patients with post-Lyme fibromyalgia syndrome as well as patients at the start of Lyme infection, before they develop fibromyalgia

#### **Initiatives**

#### Requests for Proposals

 Study of Bone Density and Biochemical Markers in the Tamoxifen Trial Launched

NIAMS and ORWH are co-funding a study to determine the effectiveness of the drug tamoxifen for preventing osteoporosis in a group of women participating in the Breast Cancer Prevention Trial (BCPT). The Bone Mineral Density and Biochemical Marker Study, a substudy of the BCPT, is being conducted at 17 clinical sites and will

involve 384 women. Tamoxifen, a drug that antagonizes the action of estrogen on the breast, has been shown in several studies to reduce bone loss in the spine in postmenopausal women with breast cancer. This will be the first study of the effect of the drug in premenopausal women and in women without breast cancer.

New Disease Registries
 NIAMS awarded four new contracts in
 1994 to establish registries for scleroderma,
 juvenile RA, juvenile dermatomyositis, and
 neonatal lupus. These registries are national
 resources of data, and patient information
 is available to the scientific community for

#### Requests for Applications (RFA)

use in basic and clinical research.

- · Basic Osteoporosis New Experimental Strategies (The BONES Initiative) In 1994, NIAMS issued an RFA that proposed new ways to approach osteoporosis. In particular, applications were sought that used new techniques and strategies based on genetics and transgenic technology, immunology, and radiologic approaches to the assessment of bone mass and bone quality. NIAMS, the National Institute on Aging, and the National Institute of Diabetes and Digestive and Kidney Diseases will be funding about 12 applications that were rated outstanding by the review group. This will provide a substantial addition to the portfolio of innovative and exciting approaches to this important public health problem.
- Osteoporosis/Related Bone Diseases Information Resource Center
  In 1994, NIAMS awarded a grant to support a resource center for osteoporosis, Paget's disease, and related bone disorders to facilitate and enhance knowledge and understanding on the part of health professionals, patients, and the public through effective dissemination of information. The teaching of osteoporosis prevention to children and adolescents and the need to reach all segments of an ethnically, economically, and geographically diverse American population have been identified as priorities.

- Basic Research in Fibromyalgia
   A NIAMS-sponsored workshop identified basic research on the pathogenesis of fibromyalgia as one critical area of future emphasis. This recommendation was the focus of the RFA, "Basic Research in Fibromyalgia," and for the subsequent funding in 1994 of five new research grants in fibromyalgia.
- Research Centers on Systemic Lupus
   Erythematosus
   In 1994, NIAMS funded two Specialized
   Centers of Research (SCORs) in systemic
   lupus erythematosus. The two new SCORs
   are located at the Hospital for Special Surgery, New York City, and at the University
   of North Carolina in Chapel Hill.

#### Conferences and Workshops

- Workshop on Chronic Pain, Pain Control, and Patient Outcomes in Rheumatoid Arthritis and Osteoarthritis, June 26-28, 1994

  The workshop was sponsored by the National Advisory Board and NIAMS. The following areas were addressed: the role pain may play as an independent component of illness, the role pain may play in preventing damage, and pain as an object of treatment.
- Disorders of the Upper Extremity,
  June 20-22, 1994

  The workshop had three major elements:
  epidemiology and workplace environment;
  pathophysiology focusing on biomechanics,
  connective tissue biology, muscle biology,
  and neuroscience; and clinical aspects. The
  perspectives of orthopaedics, physical
  medicine, and rehabilitation medicine
  were presented.

Workshop on Repetitive Motion

• Consensus Development Conference on Optimal Calcium Intake, June 6-8, 1994 The National Institutes of Health Consensus Development Conference on Optimal Calcium Intake, chaired by Dr. Lawrence Shulman, Director of NIAMS, brought together experts from many different fields including osteoporosis and bone and dental health, nursing, dietetics, epidemiology, endocrinology, gastroenterology, nephrology, rheumatology, oncology, hypertension, nutrition and public education, and biostatistics, as well as the public. The consensus panel concluded the following:

- A large percentage of Americans fail to meet currently recommended guidelines for optimal calcium intake.
- On the basis of the most current information available, optimal calcium intake is estimated to be 400 mg/day (birth to 6 months) to 600 mg/day (6 to 12 months) in infants; 800 mg/day in young children (1 to 5 years) and 800 to 1200 mg/day for older children (6 to 10 years); 1200 to 1500 mg/day for adolescents and young adults (11 to 24 years); 1000 mg/ day for women between 25 and 50 years; 1200 to 1500 mg/day for pregnant or lactating women; and 1000 mg/day for postmenopausal women on estrogen replacement therapy and 1500 mg/day for postmenopausal women not on estrogen therapy. Recommended daily intake for men is 1000 mg/day (25 to 65 years). For all women and men over age 65, daily intake is recommended to be 1500 mg/ day, although further research is needed in this age group. These guidelines are based on calcium from the diet plus any calcium taken in supplemental form.
- Adequate vitamin D is essential for optimal calcium absorption. Dietary constituents, hormones, drugs, age, and genetic factors influence the amount of calcium required for optimal skeletal health.
- Calcium intake up to a total intake of 2000 mg/day appears to be safe in most individuals.
- The preferred source of calcium is through calcium-rich foods, such as dairy products. Calcium-fortified foods and calcium supplements are other means by which optimal calcium intake can be reached in those who cannot meet this need by ingesting conventional foods.
- A unified public health strategy is needed to ensure optimal calcium intake in the American population.
- NIAMS Task Force on Lupus in High-Risk Populations, May 18, 1994
   This task force met to develop educational strategies directed to patients, the public, and

health professionals designed to improve the outcome of lupus in populations at high risk of developing the disease.

# Workshop and Small Grants Program Focused on Extending and Replicating the Results on Genetic Markers of Osteoporosis

NIAMS held a small workshop in March 1994 on the vitamin D receptor and bone density. This followed the earlier publication. of a report suggesting that common allelic forms of the vitamin D receptor predict bone density. Thus, a genetic marker that predicts who is at increased risk for fracture might be useful in identifying individuals vulnerable to the disease while they are young enough to take preventive steps. All of the participants at the workshop agreed to the urgent need for confirmation of the result Before large new studies are launched based on this finding, it was agreed to use biological material (DNA) already collected in some ongoing studies to test the hypothesis that the VDR gene plays an important role in the regulation of bone mass.

Supplements focused on the genetics of osteoporosis were solicited as part of the response to the ORWH grant supplement program. Five supplements were awarded by NIAMS and ORWH, and a follow-up meeting will be held in September 1995 to discuss the results.

#### National Arthritis Data Work Group, January 10, 1994

The work group was convened to develop current national statistics on the frequency and impact of arthritis and other musculoskeletal disorders.

#### Workshop on the Pathogenesis of Pediatric Rheumatic Diseases, September 1993

The workshop brought together clinicians and scientists in the field of pediatric rheumatic diseases to identify research opportunities that can be addressed with current methodologies. In addition to recommending the creation of disease registries, the group emphasized the need for the development of a basic research base as a fundamental step to advance understanding of the diseases.

#### Outcome Measures and Clinical Trials for SLE, September 14, 1993

The group recommended that the following outcome measures for clinical trials of systemic lupus erythematosus: add damage index, disease activity indices, measures of function or disability, organ specific measures, and cost estimates. Also recommended was a framework for more extensive collaboration among centers in the United States and other countries for the collection and pooling of data, for outcomes research, and for conducting innovative clinical trials.

#### Workshop on Early and Aggressive Therapy for Rheumatoid Arthritis, July 16, 1993

Issues identified include (1) early identification of RA cases for early and aggressive treatment, (2) recruitment strategies for cases for clinical trials, (3) outcome measures to be used, and (4) agents to be tested in combination.

Fibromyalgia Workshop, May 19, 1993
NIAMS held a workshop on the current status and future direction of fibromyalgia research. The workshop brought together a group of clinicians and scientists working in the field of fibromyalgia who developed a comprehensive list of future research activities in fibromyalgia. A summary of this workshop was published (*The Fibromyalgia Syndrome: Current Research, Future Directions in Epidemiology, Pathogenesis, and Treatment,* S. Pillemer, ed., The Harworth Medical Press, 1994).

#### Federal Working Group on Bone Diseases

This working group for Federal agencies was formed by NIAMS in 1993 in response to a congressional mandate for interagency coordination on bone diseases. Its purposes are to inform Federal agencies with responsibilities relevant to this area about their activities and to provide a mechanism for developing and conducting collaborative efforts. This group has met quarterly since 1993. Collaboration can contribute to cost savings by leveraging research dollars on investigations that lend themselves to shared resources; that build creatively on areas of mutual interest; that avoid unnecessary duplication; and that meet both the intent

of Congress and the Administration to streamline government.

#### • National Osteoporosis Data Group

The National Osteoporosis Data Group was organized in 1993 to advise NIAMS on data on osteoporosis. This includes identifying data needs, promoting the collection and analysis of data pertaining to osteoporosis, assessing the scope and impact of osteoporosis and related fractures, and promoting standards of data collection and reporting in order to strengthen the knowledge about osteoporosis. The group is composed of Federal and non-Federal scientists from the fields of epidemiology, biostatistics, health economics, clinical medicine, and biobehavioral medicine. One goal of the group is to produce a reference book, Osteoporosis in America, that will serve as a source of all the information currently available on osteoporosis.

#### NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Since its inception, the mission of the National Institute of Child Health and Human Development (NICHD) has included helping families to have healthy babies at the time they are wanted and attempting to ensure that these babies develop without disease or disability, enabling them to achieve a healthy and productive adulthood. Crucial to this mission is the basic need to expand both biomedical and behavioral knowledge concerning female reproduction, including contraception, pregnancy, and fetal development. To achieve this mission, NICHD supports a multidisciplinary research effort through a variety of program activities with a gender-specific focus.

NICHD's research in the reproductive sciences, for example, includes studying normal reproductive function as well as diseases, disorders, and conditions that affect women's health. This research helps develop knowledge that can be used to regulate fertility or treat female reproductive impairments, such as infertility. Because improving birth outcomes is one of the Institute's overall goals, maternal health during pregnancy becomes a natural focus of research. NICHD-supported researchers strive to understand prerequisites for optimal growth and development by studying nutri-

tional, neural, and hormonal controls of the reproductive process, and the roles of these controls throughout the antenatal period, infancy, childhood, adolescence, and adulthood

An additional area of NICHD research involves developing and evaluating safe and effective contraceptive methods, including female-controlled barrier methods that also may be able to protect against sexually transmitted diseases (STDs), including HIV.

Much of NICHD's behavioral research on women's health focuses on identifying social and psychological factors that affect birth planning, as well as those that impact on the transmission of HIV and other STDs. Sexual behavior and pregnancy among adolescents is an ongoing research emphasis.

#### Accomplishments

#### Reproductive Sciences

Technologic advances have enabled NICHD scientists to study fundamental reproductive processes step by step in human cells and to integrate basic knowledge with applied and clinical research. Highlights of NICHD advances from these studies, which will enhance the understanding and treatment of reproductive disorders, are described below.

For the first time, researchers have cloned the gene for synthesizing the luteinizing hormone releasing hormone (LHRH) receptor. This clone will enable scientists to further study the gene, develop new ways to influence the activity of LHRH, and design new agents to regulate fertility and treat conditions such as precocious or delayed puberty. In addition, NICHD scientists discovered that LHRH brain cells also synthesize a receptor for gamma aminobutyric acid (GABA), an inhibitory chemical produced in the brain. Future studies will focus on delineating how GABA regulates LHRH.

Inhibin, a protein normally produced in the testis and ovary, suppresses the production and release of a hormone that stimulates development of the ovarian follicle. While studying the role of inhibin in a genetically altered mouse model, NICHD-supported scientists discovered another role for inhibin, that of a tumor suppressor. Without inhibin, the mice developed testicular or ovarian tumors. Inhibin's role as a tumor suppressor may contribute to advances in preventing gonadal tumors.

During studies on the unfertilized egg, or oocyte, NICHD scientists identified carefully

timed checkpoints during maturation that indicate the quality of the oocyte and whether it is ready to be fertilized. For the first time, they also conducted similar experiments in primates.

Surface-binding molecules are necessary for the sperm to fertilize the egg. Several groups of NICHD-supported scientists discovered and characterized surface-binding molecules on the egg and sperm from sea organisms and mammals. The scientists were able to show how the binding molecules differ by species. For example, they found that a mammalian sperm-binding molecule was divided into two parts, one for fusing the sperm and egg and the other for disrupting the egg's surface membrane. The scientists also identified and characterized another binding molecule, called Sp17. This protein binds to the outer membrane of the egg and blocks fertilization.

Additional studies on binding molecules showed that the presence of the embryo in the uterus signals the uterine lining to produce specific receptors. These receptors, in turn, help bind the embryo to the lining

#### Infertility and Treatment

Excluding those who have had a hysterectomy or who are surgically stenlized, infertility affects up to 13.7 percent of U.S. women. Described below are highlights of NICHD accomplishments over the past 2 years in research on disorders and treatments related to infertility

Endometriosis is a condition in which cells lining the uterus implant elsewhere in the body. A group of NICHD-supported researchers recently found that women with endometriosis express an abnormal pattern of proteins, called integrins, involved in cell attachment and invasion. The integrin proteins may serve as important markers for diagnosis, monitoring, and treatment of endometriosis.

Women with premature ovarian failure have high blood levels of luteinizing hormone (LH), which suppresses ripening of the egg. In addition to testing drugs that reduce high blood levels of LH, NICHD researchers recently engineered a mouse model that produces high levels of LH. This model will help examine two other conditions associated with infertility, polycystic ovarian syndrome and granulosa cell tumors.

NICHD studies compared the standard therapy for treating women with LHRH deficiency, exogenous gonadotropin injections, with a newer protocol of intravenous pulsatile LHRH The newer protocol produced less ovarian

enlargement; improved the chances of conception by 24 percent over the standard treatment; cost \$200 to \$2,600 less per cycle than gonadotropin injections; and was less likely to result in multiple gestations, which compared to the hospital cost of \$3,600 per single birth could cost \$6,300 per twin birth and \$13,300 per triplet or higher birth.

#### Women's Contraceptive Options

NICHD supports an array of research on women's contraceptive options, some of which are designed to prevent both pregnancy and STDs. Below are selected NICHD advances related to developing, improving, and assessing the safety of contraceptive products and increasing their availability to women.

In a primate model, NICHD-supported scientists conducting basic research in vaginal biology showed that the cervix is not required for simian immunodeficiency virus (SIV) transmission; that is, the virus can pass through the vaginal wall. Furthermore, the scientists found that seminal fluid enhanced the transmission of SIV.

The successes and shortcomings of longacting, progestin-based contraceptive devices, such as Norplant, have fostered research on other implantable systems. NICHD completed research on Capronor, a long-acting biodegradable implant, and is working with Wyeth-Ayerst to commercialize the device.

To improve the understanding of disease transmission and unintended pregnancy in the United States, NICHD launched an initiative on unplanned pregnancy to study, in part, decisionmaking and the use of barrier contraceptives among women. Basic trends concerning the use of different methods to prevent STDs and pregnancy are currently being monitored through the National Survey of Family Growth (an existing national survey) and through other surveys of adolescent and young adult health risks. (See also the section on Behavioral Issues: Fertility-Related Behaviors.)

NICHD launched an initiative on female-controlled barrier contraceptives that supports studies identifying physical and chemical products that may offer women ways to protect themselves against pregnancy and STDs without negotiating condom use. As a follow-up to the 1993 licensing of the female condom, NICHD launched a comparative study of all marketed barrier contraceptives, including the female condom, for their ability to prevent pregnancy

and STDs. In addition, the female condom was added to an intervention study originally targeting minority women to help understand sexual behavior, decisionmaking, and skills in negotiating the use of barrier contraceptives.

In 1993, NICHD released a program announcement for studies on antiprogestins and funded several projects designed to improve knowledge about different uses for antiprogestins, such as treating gynecologic disorders and providing contraception. In 1994, the Institute released a request for proposals for research on designing, synthesizing, and testing antiprogestins with fewer side effects and greater potency than the most frequently used antiprogestin, mifepristone.

NICHD funded a clinical trial to test whether administering prophylactic antibiotics would reduce pelvic inflammatory disease or other events that could cause subsequent removal of intrauterine devices. The results showed no difference in the proportion of women in the treatment group and placebo group that had intrauterine devices removed for medical reasons.

The results of several NICHD-supported studies focus on the estrogen component of oral contraceptives and the link between oral contraceptives and the development of chronic diseases. The NICHD-supported National Health and Nutrition Examination Survey Epidemiologic follow-up study showed that cardiovascular mortality was reportedly reduced among postmenopausal women using oral contraceptives and/or estrogen replacement. In two additional studies, NICHD found that (1) smoking among users of oral contraceptives was linked to a greater risk for developing ovarian cysts and rheumatoid arthritis and that (2) past or current use of oral contraceptives reduced the risk of rheumatoid arthritis in women under age 45 by about 30 percent, with even greater protection associated with longer use.

#### Pregnancy and Perinatology

NICHD supports a multidisciplinary research program in pregnancy and perinatology. In addition to studying normal developmental processes, researchers explore complications associated with pregnancy that lead to negative birth outcomes. These studies have yielded an array of findings in such areas as nutrition during pregnancy, fetal maturation and development, and prenatal diagnosis and monitoring. Over

time, knowledge from these efforts should improve pregnancy outcomes and decrease infant mortality, especially in more high-risk populations.

NICHD-supported studies showed that zincdeficient women have poor pregnancy outcomes. For example, in one study of pregnant black women with low zinc levels, zinc supplements appeared to decrease preterm delivery and infection and improve fetal growth.

NICHD scientists have demonstrated that folate supplements during the early period of fetal development can help prevent neural tube defects such as spina bifida. Based on these findings, the Food and Drug Administration is currently recommending that cereals be fortified with folic acid at levels of 140 µg per 10 grams of cereal, including pasta and rice. In addition, the Public Health Service has recommended that all sexually active women of childbearing age take 0.4 mg of folic acid as a daily supplement.<sup>1</sup>

Pioneering fetal surgery research has perfected techniques for repairing a serious congenital anomaly of the pulmonary system.

Related efforts demonstrating that the early fetus heals without scarring promise to reveal approaches to minimize scarring in adults.

The NICHD Neonatal Research Network has demonstrated that antenatal steroids reduce by 50 percent or more the risk of death and severe bleeding into the brain of very-low-birthweight infants, subsequently reducing the length and cost of hospital care. At present, less than 20 percent of women who deliver very-low-birth-weight infants receive antenatal steroid treatment. Other NICHD-funded researchers have determined that antenatal steroids also enhance the efficacy of postnatal surfactant replacement. Ongoing clinical trials are exploring the potential of other antenatal treatments, such as a thyroid-releasing hormone to reduce lung disease and phenobarbital to prevent bleeding into the brain of premature infants. (See also the section on conferences/ workshops for a description of the consensus development conference, "Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes.")

Researchers recently discovered that placental proteins called "lactogens" affect fetal growth and maturation. Future research on their structure, function, and mechanism of action may be especially useful for modulating fetal growth and birth weight.

Researchers are also working on developing intrauterine surgical techniques designed to correct abnormal fetal development prior to delivery.

A large, randomized, controlled trial of lowrisk pregnant women evaluated the routine use of prenatal ultrasound screening. The study showed that the routine use of two screening sonograms failed to reduce the incidence of perinatal morbidity or mortality in low-risk pregnancies when compared to the selective use of ultrasound to form clinical judgment. The findings revealed that the adverse perinatal outcome rate was essentially the same for both groups, as was the rate of preterm delivery and the birth weight distribution. In addition, while selective use of sonograms is beneficial, their routine use in the United States continues to add considerable cost to prenatal care without improving perinatal outcomes. Studies show that if clinicians performed only those ultrasounds that were clinically indicated for lowrisk women, the Nation could save \$80 million annually in sonography costs alone. More than one-fourth of these dollars, or \$22 6 million, would accrue to Medicaid and other government programs

Studies have revealed that color Doppler ultrasound is effective in the noninvasive evaluation of fetuses suspected of having congenital anomalies, especially anomalies that lend themselves to surgical remediation (e.g., the placement of shunts). This new ultrasound is also useful for evaluating the uterine and fetal circulation in patients with preterm labor or intrauterine growth retardation. (See also the section on conferences/workshops for a description of the workshop, Computer-Assisted Imaging of Embryonic and Fetal Development.)

<sup>&</sup>lt;sup>1</sup> Most recently, an NICHD research team has identified the metabolic defect that may be responsible for the majority of cases of newal tube defects (NTDs). While it was known from earlier research that folic acid could prevent NTDs, the new study offers a possible explanation as to why. It also suggests that administering folic acid does not merely correct a deficiency, but that women at risk for having a child with an NTD may have a metabolic abnormality requiring additional folic acid.

#### Preventing Preterm Labor and Adverse Birth Outcomes

Preterm delivery is a major cause of infant sickness and death. Disorders related to short gestation and low birth weight are the second leading cause of neonatal death. Approximately 300,000 infants of less than 36 weeks gestation are born each year in the United States, many of whom require treatment in neonatal intensive care units (NICUs) for complications related to preterm birth. NICU costs for one preterm infant weighing less than 2.2 pounds can easily exceed \$200,000. Highlights of NICHD-supported efforts over the last 2 years related to infant mortality, premature labor, and preterm births are summarized below.

NICHD supported a randomized trial to clarify prior research results on the benefits of administering prophylactic aspirin to pregnant women. The group taking daily aspirin experienced only a marginal decrease in the incidence of preeclampsia, a toxemia of late pregnancy. Furthermore, this group of women also experienced a significant increase in the incidence of abruptio placentae, early placental detachment from the uterus that threatens the life of both mother and baby. Thus, the researchers recommended against taking daily aspirin to prevent preeclampsia.

NICHD researchers demonstrated that the incidence of very-low-birth-weight infants among pregnant black women can be largely attributed to the health status of the women. Maternal conditions known to trigger labor or indicate the need for medical attention occurred more often among black mothers than among white mothers. These results will help explain how social and economic conditions contribute to poor maternal health, and why black women are three times more likely than white women to give birth to very low birth weight infants.

NICHD issued a request for applications (RFA) designed to promote further research on the social, behavioral, and cultural factors that affect infant and child health among Hispanic populations. Four of the five projects resulting from the RFA focus on infant mortality. These include studies of the factors affecting infant health outcomes among Mexican and Mexican-American populations, and a large-scale study of Puerto Rican infant health. (See also the section on Behavioral Issues: Impact of Maternal and Family-Related Characteristics on Child Development.)

Considerable evidence suggests that poor birth outcomes, such as late fetal deaths, verylow-birth-weight, preterm delivery, and smallfor-gestational-age births, are associated with delayed childbearing—that is, women giving birth to their first child when they are 30 years of age or older. Researchers sought to evaluate whether the increased risks associated with delayed first births were due to medical and obstetrical complications associated with maternal age or to characteristics of a subgroup of women among those who delayed childbearing and experienced difficulties in conceiving. Study findings indicate that problems in conceiving (or histories of infertility) could not account for the increased risk of poor birth outcomes among women who delayed childbearing. Instead, the increased risk of poor birth outcomes was most strongly associated with increased maternal age. This association was significant, even after controlling for such factors as pregnancy complications, smoking, or level of the mother's education. The findings suggest that independent factors associated with increased maternal age for first births affect poor birth outcomes.

An NICHD-supported randomized trial of antibiotics used in women experiencing premature rupture of membranes will assess the effectiveness of the antibiotics in preventing preterm birth and reducing newborn complications.

The Intramural Perinatology Research Branch was established to focus research on the events responsible for the extraordinarily high incidence of infant mortality in the District of Columbia and among other inner-city populations. In recent branch efforts to understand the difficulties associated with treating suspected cervical incompetence in third trimester pregnancies, NICHD researchers found that more than half of the women studied had an infection in their amniotic fluid. They also discovered that cytokines are markers for amniotic infection, and they have developed a highly sensitive laboratory test to detect elevated cytokine levels in the presence of asymptomatic amniotic infection. This development, in turn, could permit early treatment and prevent premature labor.

As part of several recent initiatives to address infant mortality, NICHD is trying to isolate factors associated with preterm labor and test ways to prevent it. In one study, researchers

hope to identify markers for preterm labor by using home uterine monitors to compare contraction frequency and patterns in women with and without preterm labor.

#### Behavioral Issues: Fertility-Related Behaviors

Knowledge about a variety of behaviors, such as sexual activity, contraceptive use, and other fertility-related behaviors, is essential to the health and well-being of individuals and society. It is crucial to understand the behavior that puts people at risk of an unintended pregnancy or at risk of failing to conceive when they want to. As a result, a significant part of the NICHD behavioral research portfolio targets studies on the determinants, correlates, and consequences of fertility and fertility-related behaviors. Additional studies focus on adolescent pregnancy and the association between poverty and teen births, as well as research on communication dynamics, role modeling, and social skills development.

NICHD-supported studies continue to examine motivational factors in birth planning to better understand what influences women have to prevent births and to give researchers more sensitive methods for measuring these motivations. Scientists have found that improved motivational factors are effective predictors of contraceptive vigilance in a sample of sexually active, inner-city adolescent girls.

NICHD is funding a number of studies that provide insights into the determinants of condom use, including the woman's role in negotiating condom use among sexually active couples. Several studies indicate that condom use varies by factors such as race, ethnicity, age, and marital status. The nature and duration of relationships, including gender ideology (the degree of adherence to traditional sex roles and attitudes) are also important predictors of couples' condom use, as are specific HIV-risk behaviors.

Findings from recently conducted research may have implications for developing intervention programs for the prevention of early, out-of-wedlock childbearing. For example, the results of one study indicate that an adolescent female who has been raised by a single mother in a stable household may be less likely to become a single mother herself than an adolescent who has experienced frequent changes in family structure.

NICHD initiated, with support from other NIH institutes, the first nationwide, longitu-

dinal study of the determinants of adolescent health known as Add HEALTH, Behaviors that promote or are detrimental to health. will be explored (including, but not limited to, smoking, exercise, nutrition, drinking, fighting, seat belt and helmet use, and contraceptive use), in addition to community factors that may influence health outcomes, such as peers, family members, and specific community characteristics. A unique aspect of the study is its focus on how health-related behaviors of adolescents are affected not only by their own individual skills, attitudes, and beliefs, but by the opportunities and restraints imposed by their social and physical environments. Add HEALTH is the first study to select the large and diverse sample that is needed to measure the effects of community characteristics on adolescent behaviors. Populations targeted for oversampling include Cuban, Puerto Rican, Chinese, high-income African-American, and disabled adolescents.

NICHD-supported researchers are developing education programs to encourage parentteen communication about premarital sexual intercourse and birth control. These studies investigate the dynamics of such communication and identify variables in low-income black families that predict teen sexual behavior and inconsistent birth control use.

Findings from NICHD-supported studies reveal that greater communication, higher levels of self-esteem, and self-reliance of female partners correlate with safer sexual practices. Thus, prevention interventions that inform, build communication skills, and emphasize role modeling may be effective in lowering risky sexual behavior.

#### Behavioral Issues: Impact of Maternal and Family-Related Characteristics on Child Development

The Institute also supports research on the effects of maternal and family-related characteristics on the growth and development of infants, children, and adolescents. Recent projects examined a wide range of issues, including maternal responsiveness and child development, caregiving practices, domestic violence, and adolescent pregnancy.

In response to the growing need for coordinated research to fully use existing sources of data, NICHD launched a new, 5-year, multidisciplinary research network designed to examine family and child well-being. The

network has already been successful in creating a research agenda that emphasizes the role of fathers in child well-being, as well as the role of social resources and other contextual influences on the functioning of families and the well-being of children. These efforts are aimed at making Institute-sponsored behavioral research more relevant to current public policy issues.

Recent NICHD studies treat the interaction between maternal characteristics and behaviors and the development of infants and children. For instance, one group of intramural scientists demonstrated that three skills characteristic of cognitive functioning at 5 months of age predict later childhood mental ability. It was found that infant perceptual-cognitive ability at 2 months of age, maternal I.Q., and maternal responsiveness to the 5-month-old infant each contribute to the expression of cognitive skills in the 5month-old. Therefore, variation in the information-processing ability of children may be explained, in part, by specific infant and maternal factors that are evident soon after birth. These studies are important in that they allow an assessment of the impact of a child's very early environment, positive or negative, on his or her genetic endowment of cognitive skills.

Additional intramural studies examined the effects of different types of caregiving practices on human infant and child social and emotional development as well as cognitive competence. One study involves a long-term follow-up of a sample of Swedish children who have been raised since 16 months of age in a day care center, in home day care, or at home with one or both parents. Previous analyses demonstrated that the type of early child care arrangement does not predict individual differences in either aggression or obedience, whereas the quality of early home care is a strong predictor of both. In 1993, it was found that measures of personal maturity and verbal ability are significantly affected by the type of care received, home day care being associated with the lowest scores.

A particularly interesting finding in a longterm study of the effects of domestic violence on children was that mothers who themselves were abused were much more likely to report problems in the behavior of their abused children than mothers who were not abused.

#### Vertical Transmission of AIDS

NICHD funds a variety of research projects aimed at promoting treatment and preventing

the transmission of HIV/AIDS in women, infants, children, and adolescents. This research includes epidemiologic and natural history studies, as well as therapeutic research and clinical trials. Other AIDS-related efforts involving dual-purpose contraceptives and behavioral studies were discussed earlier.

NICHD-supported studies in Africa are evaluating vitamin A and micronutrient supplementation for HIV-infected pregnant women as a way to reduce perinatal transmission and supplementation for infected children as a way to slow HIV progression. Recent findings indicate that HIV-infected women who transmitted HIV infection to their infants had significantly lower vitamin A levels than those who did not transmit, with suggestion of a dose-response relationship between vitamin A levels and risk of transmission.

NICHD also started an important study in Kenya to evaluate the role of breast milk in perinatal HIV transmission and compare it to any transmission of HIV that could be associated with bottle feeding in developing countries. A number of other studies, including one completed with Rwandan women, have shown that breast milk is more likely to be positive for HIV within 2 weeks after birth than 14 weeks after birth.

A phase III clinical trial jointly funded by NICHD, the National Heart, Lung, and Blood Institute, and the National Institute of Allergy and Infectious Diseases (NIAID) is evaluating the effectiveness of hyperimmune HIV immunoglobulin (HIVIG) in reducing perinatal HIV transmission among infected pregnant women with more advanced disease than those enrolled in the AIDS Clinical Trials Group (ACTG) 076 (see below). To date, almost 100 of the 800 planned participants are enrolled (50 percent from the NICHD network); initial studies have shown that HIVIG has pharmacokinetics similar to intravenous immunoglobulin and is well-tolerated.

A collaborative effort between foreign institutes, NICHD, and NIAID on the ACTG 076 study revealed compelling evidence that zidovudine (ZDV) given during pregnancy and labor and for a short time to the newborn infant can reduce perinatal HIV transmission from infected pregnant women by 67 percent. The treatment regimen consisted of ZDV administered to HIV-infected pregnant women beginning between 14 and 34 weeks of gestation, continued intrapartum, and then to their

infants during the first 6 weeks of life. This is an important finding because it is the first indication scientists have had that a drug intervention can block the transmission of HIV

Based on this evidence, NICHD led a Public Health Service task force to develop recommendations on the use of ZDV to reduce perinatal transmission of HIV. In addition, because the long-term effects of using the drug are unknown, two joint NICHD/NIAID studies were started to evaluate the ZDV regimen for any long-term adverse consequences: (1) ACTG 219 provides intensive follow-up through age 21 years for infants born to mothers enrolled in ACTG 076, and (2) ACTG 288 evaluates the clinical and virologic status of women enrolled in ACTG 076 for the 3 years following the birth of their infants.

The NICHD Mothers and Infants Cohort Study (MICS), begun in 1985, continues to yield findings that describe the rate of vertical transmission, factors affecting this transmission, and the impact of HIV infection on the growth and neurodevelopmental outcomes of infected infants. Recent data indicate that prolonged labor with ruptured membranes may be associated with increased risk of vertical transmission This is important for understanding the timing and mechanisms of vertical transmission and for evaluating potential interventions, such as Cesarean delivery or virucidal vaginal cleansing at delivery. Other analyses show that infected children with advanced HIV-related symptoms appear at much higher risk for serious developmental impairments compared with infected children with lesser symptoms who manifest relatively normal neurodevelopment. These results may aid the development of costeffective ways to monitor and treat children born to HIV-infected women and enhance the design of clinical trials.

Building on the MICS study, NIAID and NICHD collaborated on The Women and Infants Transmission Study (WITS), which has enrolled 1,100 women and their offspring. With an emphasis on integrating epidemiological and molecular approaches, the WITS addresses both pathogenic and public health issues. Recent data analyses show a relatively high prevalence of Mycobacterium tuberculosis infection (14 percent) in this cohort of HIV-infected women, that diagnosis of HIV infection in infants may be made using HIV culture by 6 months of age, and that the presence of immune activation markers at birth correlates

with early HIV-culture positivity and a more rapid decline in CD4+ cell counts in these infected infants.

Women's Health and Disabled Populations As part of its mission, NICHD sponsors studies that enhance the health, productivity, independence, and quality of life of persons with disabilities. Because women generally outlive men and many disabilities are associated with the aging process, a portion of the Institute's research on disabilities focuses on slowing the rate of deterioration and restoring functioning in women. Further studies explore issues related to sexuality concerns among disabled women.

NICHD has started a longitudinal study to identify early decrements in physical functioning in women age 65 or older and to determine whether these changes can predict future disability. Scientists are seeking to identify those older women at increased risk of becoming disabled and to develop interventions that could help prevent disability in aging women.

Another NICHD study examines the influence of medical and psychosocial factors on survival and recovery of hip fracture patients over the age of 65. Variables under evaluation include restoration of physical capacity, functional independence, and social interaction during the year following a hip fracture. Although many medical factors influence recovery, this research focuses on those determinants of recovery that could be modified, such as preoperative medical and cognitive status, peri- and post-operative complications, family and friend involvement in recovery, and therapeutic interventions.

Little information exists concerning the impact of disabilities on women's sexuality and their quality of life. NICHD supported a national survey to provide information on (1) these women's views of themselves as sexual individuals, (2) the quality of their gynecological and related health care, and (3) their success in establishing fulfilling personal relationships. Initial results indicate that women with disabilities experience a much higher level of abuse than was anticipated, encounter many societal barriers to normal sexual development, and access gynecological and other women's health care services less frequently than the general population.

Two NICHD-supported studies, focusing on the physiological responses in women after

a spinal cord injury (SCI), provide a unique opportunity to improve the quality of life of women with SCI. For example, both pain and spasticity are important secondary conditions associated with SCI. Studies to date, however, show that residual sensory and perceptual reactions to birth canal stimulation help reduce pain and spasticity while eliciting a sexual response in women with SCI.

#### Conferences/Workshops

- Development of Topical Microbicides, May 24-26, 1993, in Bethesda, MD

  This workshop, co-sponsored by NICHD, NIAID, and the Food and Drug Administration, was planned to aid the development of a research agenda involving needs for basic and clinical studies. Groups discussed preventing the transmission of viruses and microbes. The workshop also highlighted the difficulties inherent in developing new products and encouraged further testing of existing products.
- Research on HIV Transmission Through Breastfeeding, June 24, 1993, in Rockville, MD

  This workshop, co-sponsored by NICHD and NIAID in collaboration with the Office for Protection from Research Risks, reviewed and discussed the risk factors and ethical concerns associated with HIV-transmission by HIV-positive mothers through breast-

feeding. Both public policy and research

issues were discussed.

Ethical Considerations in International

 Ultrasound Screening: Implications of the RADIUS Study, December 3, 1993, in Rockville, MD
 Participants in this interpretive workshop co-sponsored by the Office of Medical Applications of Research (OMAR), speculated on how the RADIUS (Routine Antenatal Diagnostic Imaging Ultrasound Study) results might affect public health and reimbursement policies on routine obstetric ultrasound screening. The development of a policy position was not an objective of

the workshop. Rather, the participants

sought to provide insight on routine ultra-

sound screening to decision-makers and

policymakers from a wide variety of

disciplines and organizations.

Maturation on Perinatal Outcomes,
February 28-March 2, 1994, in
Bethesda, MD
The broad conclusion resulting from this conference, co-sponsored by NICHD, the National Heart, Lung, and Blood Institute, the National Institute on Nursing Research (NINR), and OMAR, was that antenatal corticosteroid therapy is indicated for women at risk of premature delivery with

· Effect of Corticosteroids for Fetal

result in a substantial decrease in neonatal morbidity and mortality, as well as in substantial savings in health care costs.

• Technical Review of Interventions to Reduce Vertical HIV-1 Transmission, April 5, 1994, in Washington, DC The purpose of this workshop, co-sponsored by NICHD and the American College of Obstetricians and Gynecologists (ACOG), was to inform members of ACOG about the

few exceptions, and that this therapy will

- Obstetricians and Gynecologists (ACOG), was to inform members of ACOG about the results of ACTG 076 and to discuss other factors (such as Cesarean section and vaginal cleansing) that may affect mother-to-child transmission of HIV. Policy implications for research on obstetric care were explored.

   Health of Women with Physical
- Disabilities, May 9-11, 1994, in Bethesda, MD

  This conference, co-sponsored by NICHD, ORWH, NINR, the Agency for Health Care Policy Research, the Centers for Disease Control and Prevention, the National Institute of Dental Research, and Paralyzed Veterans of America, highlighted the health needs of women with disabilities and provided research directions for improving the health of women with disabling conditions.
- Alternatives to Hysterectomy:
  Bench to Bedside, May 23-24 1994,
  in Bethesda, MD
  This workshop, co-sponsored by NICHD
  and ORWH, included updates on progress
  from investigators supported under the 1992
  initiative on endometriosis and uterine
  fibroids. The group also explored future
  research directions. Particular emphasis
  was given to treatments that preserve
  fertility potential.

 Computer-Assisted Imaging of Embryonic and Fetal Development, June 23-24, 1994, in Bethesda, MD

Presentations and discussions at this workshop allowed the formulation of future goals for embryo and fetal imaging. These goals are aimed at enhancing the ability to detect and treat birth defects, facilitating research on the causes of birth defects, and enabling advanced training of obstetricians. The participants recommended steps to be taken to begin working toward these goals.

Initiatives: Request for Applications/ Program Announcements/Request for Proposals (RFA, PA, RFP)

#### FY 1993

CA/HD-93-033

Rehabilitation and psychosocial research in younger women with breast cancer (NCMRR/ARMRB)

PA 93-048

Basic and applied studies on antiprogestins (CPR/CDB)

PA 93-085

Research involving human in vitro fertilization

PA 93-085

Biological factors influencing sexual transmission of HIV (NICHD/NIDDK)

RFP 93-02

Prostaglandin excretion in preeclampsia (DESPR)

RFP 93-08

Female condoms/STD prevention (CPR/CAREB)

RFP 93-12

Fertility drugs and ovarian cancer (CPR/CAREB)

RFP 93-13

Perinatal transmission of HIV (CRMC/PAMAB)

#### FY 1994

HD-94-004

Genetics and physiology of human oocytes (CPR/RSB)

DK-94-009

Research on HIV infection in the genitourinary tract (CPR/RSB)

HD-94-016

Cooperative multicenter reproductive research network (CPR/RSB)

HD-94-017

Vaginal immunology: Interaction with intravaginal products (CPR/CDB)

HD-94-018

Vaginal physiology: Interaction with intravaginal products (CPR/CDB)

HD-94-023

Unintended pregnancy in the United States (CPR/CDB/RSB)

HD-94-023

Uterine bleeding and steroid hormones (CPR/CDB)

Al-94-023

Mechanisms of embryonic/fetal-maternal tolerance (NICHD/RSB/DBGTB)

RFP 94-05

Paradigms for U.S. fertility research (CPR/DBSB)

RFP 94-13

Antiprogestional agents testing (CPR/CDB)

RFP 94-14

Synthesis and development of new spermicides with microbicidal properties (CPR/CDB)

NCMRR = National Center for Medical Rehabilitation Research

ARMRB = Applied Rehabilitation Medicine Research Branch

CPR = Center for Population Research

CDB = Contraceptive Development Branch

DESPR = Division of Epidemiology, Statistics and Prevention Research

CAREB = Contraceptive and Reproductive Evaluation Branch

PAMAB = Pediatric, Adolescent and Maternal AIDS Branch

CRMC = Center for Research for Mothers and Children

RSB = Reproductive Sciences Branch

DBGTB = Developmental Biology, Genetics and Teratology Branch

DBSB = Demographic and Behavioral Sciences
Branch

## NATIONAL INSTITUTE OF DENTAL RESEARCH

The National Institute of Dental Research (NIDR) sponsors research on diseases and disorders of the teeth, mouth, jaws, and face, including systemic diseases with oral complications. The mouth is now viewed as an accessible, noninvasive laboratory in which to (1) study the general health and diseases of the body, (2) measure the presence in saliva of substances and biomarkers of diseases, and (3) exploit gene therapy to repair damaged salivary glands and use healthy salivary cells to secrete therapeutic agents. As women's oral health issues come into focus, new research opportunities emerge.

#### Accomplishments

#### Women's Oral Health Research

Women are living longer than men, making up an increasingly larger portion of the elderly population. With this sex advantage, however, comes significant general morbidity, including oral health problems. As people age, they are vulnerable to a host of diseases and conditions osteoporosis, cancers, stroke, arthritis, and diabetes mellitus-that affect oral health. Unfortunately, treatments for some of these conditions may further compromise oral tissues. Epidemiological data indicate that women experience greater tooth loss at an earlier age, greater salivary dysfunction, and more chronic orofacial pain than do men. Likewise, clinical impressions suggest that the prevalence of atrophic mandibles (jaw bone) and diseased periodontia that resist treatment is higher in women than in men. Some researchers believe that these conditions are promoted by female hormones, especially estrogen. Estrogen is known to exert positive and negative influence on tissues throughout the body, including oral tissues such as the oral mucosa, salivary glands, temporomandibular (jaw) joint, and bone. Such influence may be explained by the discovery that salivary glands, temporomandibular joints, and bone have estrogen receptors. The implications of these discoveries have opened up an exciting field for research.

#### Gingivitis

The gingiva surrounding the crown of the tooth can become red and swollen, and can bleed when infected with certain oral bacteria. This condition is called gingivitis. Gingivitis can also be triggered or exacerbated by hormones. For example, gingivitis may occur immediately before a women menstruates and clear up once menstruation has begun. Pregnant women and those on oral contraceptives may also experience increased swelling. In these cases, gingivitis is transient and not connected with significant loss of attachment of teeth to bone.

#### Oral Cancer

Demographic patterns of behavior are important indicators of emerging morbidity and mortality in women. For example, more schoolage girls are smoking than boys. If this trend continues, there will be significantly more oral cancers found in these women as they age. The ORWH has contributed supplemental funding to an NIDR-sponsored oral cancer project: Metabolic Epidemiology of Oral Cancer in Women.

#### AIDS and Oral Health

Another behavioral trend shows some women frequently engaging in unprotected sex, which has resulted in women now constituting the fastest growing population with HIV. Oral lesions are among the important early manifestations of HIV disease in both males and females. NIDR conducts basic, clinical, and epidemiological research on HIV infection/AIDS that includes men, women, and children as research subjects.

One of the outstanding achievements in 1994 by an NIDR intramural team was the identification of a protein in human saliva that blocks HIV from infecting white blood cells. The discovery may help to explain why AIDS is virtually never transmitted orally. The protein secretory leukocyte protease inhibitor (SLPI) is thought to attach to the surface of white blood cells, thereby blocking their infection by HIV. The next step is to identify the SLPI receptor and determine the role it plays in HIV entry into host cells.

In Fiscal Year 1993, NIDR issued a request for applications to support an oral component in a study of the National Institute of Allergy and Infectious Diseases (NIAID), the Women's Interagency HIV Study (WIHS), a prospective, multisite study to investigate the clinical, immunological, virologic, and behaviorally associated aspects of HIV disease progression in women. NIDR is supporting an oral component at five WIHS sites to document the oral manifestations of HIV infection. In Fiscal Year 1995, NIDR will increase its funding for the oral component to allow for more detailed

analyses, collection of tissue samples, and comparisons of oral lesions with lesions at other mucosal sites

ORWH has contributed supplemental funding to two NIDR-supported AIDS projects: (1) Oral Findings in HIV Infection: Different Risk Groups and (2) HIV Inhibitory Factors in Human Saliva.

#### Inflammatory Diseases Research

Inflammatory diseases, such as Sjögren's syndrome (SS) and rheumatoid arthritis, are found more frequently in women. For this reason, many believe these conditions are influenced by hormones.

Sjögren's Syndrome and Dry Mouth

SS is an inflammatory, autoimmune disease that causes destruction of salivary and tear glands. Ninety percent of cases are found in women. Lack of saliva can cause rampant tooth decay, tooth loss, and oral sores. In addition, xerostomia (dry mouth) makes speaking and swallowing difficult. Inflammatory disease is not the only cause of oral dryness; others include radiation therapy for head and neck cancers and chemotherapy. In the aging population, the most prevalent cause of dry mouth is the use of medications. NIDR scientists have shown that the aging process itself does not cause oral dryness.

Until recently, the age of onset for SS was thought to be over the age of 40. NIDR investigators, however, are diagnosing the disease in much younger women, probably because symptoms are being recognized earlier. Rheumatology is the medical specialty to which SS is assigned; nevertheless, patients with dry mouth or eyes might just as easily be diagnosed by dentists and ophthalmologists. Since SS is chronic and progressive, it is of the utmost importance that patients be diagnosed as early as possible so there is opportunity to intervene, forestall, or delay the destructive process.

NIDR conducts and supports both basic and clinical research on xerostomia. Basic research is focused on discovering the mechanisms through which salivary glands are destroyed. The NIDR Division of Intramural Research operates a dry mouth clinic where patients are referred for diagnoses and assignments to treatment protocols. The protocols include drugs that stimulate salivary gland secretion and drugs that treat the underlying chronic inflammation.

NIDR intramural scientists are looking for biomarkers in the saliva that signal salivary gland destruction so that invasive biopsy might be avoided. The next step would be to develop a biological response modifier to stop or reverse salivary gland response to the underlying inflammatory condition.

Recent studies conducted by scientists at NIDR and the National Heart, Lung, and Blood Institute have shown how the salivary gland can be used as a target for gene therapy. This approach offers the possibility for not only repairing diseased or damaged salivary glands but also for enabling the glands to produce therapeutic drugs for delivery into the mouth or general circulation. NIDR scientists are developing animal models for testing these new drugs and procedures.

ORWH supplemented the development of the animal model and helped to fund an extramural project on SS xerostomia

#### Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory process of unknown etiology that begins in youth or middle age. RA is characterized by joint inflammation; tendons, ligaments, fascia, muscle, and bone also may be jeopardized by the inflammatory process. The disease affects women three time more often than men.

NIDR intramural scientists have shown that nitric oxide, an endogenous gas known to have many beneficial effects in the body, contributes to the development of rheumatoid arthritis and other inflammatory diseases. Using an arthritis rat model, a team of NIDR scientists detected abnormally high levels of nitric oxide production in inflamed joints. Treatment with a drug that inhibits nitric oxide formation suppressed arthritis in the animals. These findings point to nitric oxide as both a contributing factor in chronic inflammation and a target for therapeutic agents.

Other NIDR intramural scientists have successfully treated arthritic rats by blocking the action of a molecule that regulates the body's response to infection or tissue injury. The molecule transforming growth factor-beta (TGF-B) is a multifunctional molecule that plays a pivotal role in switching the immune system on and off. In the early stages of an infection, TGF-B is secreted by white blood cells and acts as a signal that attracts other white cells to fight the infection. As the infection subsides, TGF-B reverses its role and sup-

presses the activity and recruitment of white cells. However, in chronic diseases, such as RA, the normal cycle of events does not occur, and TGF-B continues to attract white cells. It is the excessive accumulation of white cells that produces red, swollen joints and eventually leads to tissue destruction. When an antibody that inhibits TGF-B was injected directly into the animals' joints, arthritis symptoms were greatly reduced. The researchers believe this antibody may provide a mechanism for treating arthritis and other chronic inflammatory diseases.

#### Angiogenesis

The NIDR intramural program supports research that suggests that estrogen stimulates the sprouting of new blood vessels from mature ones (angiogenesis) by promoting cell attachment, migration, proliferation, and differentiation. This finding may have implications for wound healing, tumor growth, and inflammatory diseases.

Tissues exhibit an increase in blood vessel formation under certain conditions, such as wound healing and tumor growth. It also occurs in certain inflammatory diseases, such as RA, where small new vessels invade and damage joint cartilage. Other inflammatory diseases found most commonly in women include systemic lupus erythematosus, Takayasu's arteritis, and SS. Inflammation of oral tissues, as stated, is also more frequent and more severe in women who are pregnant or using oral contraceptives. Angiogenesis at breast tumor sites is also being studied as a marker of metastatic risk. Conversely, it is speculated that vascular cell growth and migration enhanced by estrogen may be factors in protecting premenopausal women from heart disease.

The more scientists learn about angiogenesis and its link with estrogen at the cellular level, the closer they will come to controlling its damaging effects, mobilizing it to enhance tissue health, and finding ways to use it as an indicator of biological stress.

#### Pain Research

The NIH Pain Research Clinic, under the directorship of NIDR, brings researchers and dental, medical, and nursing professionals together to study pain and find new ways to assess, diagnose, and treat it.

The NIH Revitalization Act of 1993 addresses the issue of chronic pain, asking NIDR to

take the lead in the development of a report to Congress on the frequency and associated health care costs for seven chronic pain conditions, including temporomandibular disorders.

#### Temporomandibular Disorders (TMDs)

TMDs are conditions of chronic pain and dysfunction that affect either the temporomandibular (jaw) joint (TMJ) and/or the muscles that control chewing. Epidemiological studies reveal that twice as many women as men report having experienced jaw joint and/or face pain more than once during a previous 6-month period. Based on survey data, an estimated 3.5 million people will seek health care for TMD symptoms in the next 6 months in an estimated 6:1 female to male ratio. In addition, at least 20,000 patients received alloplastic implants to relieve their conditions between 1985 and 1992, and this is a conservative estimate. In many cases, the implants have failed, causing further damage and unrelieved, excruciating pain.

NIDR supports research on TMDs through its intramural and extramural programs and through a series of initiatives. Over the last 26 years, NIDR's TMD research portfolio has grown to represent half the Fiscal Year 1994 NIDR pain portfolio and 2 percent of the entire NIDR research budget. A sampling of four findings from currently funded research projects is highlighted below.

Data from a randomized clinical study comparing surgical and nonsurgical treatments for one type of TMD disorder indicate that patients receiving nonsurgical treatments are experiencing outcomes equivalent to, or better than, those receiving surgery.

The NIDR-funded Research Diagnostic Criteria for TMDs have been judged extremely reliable. An application to evaluate their validity is under review.

An NIDR-sponsored research project has resulted in the identification of the miniature pig as a excellent animal model for TMD research. Its structure and masticatory patterns are surprisingly similar to that of the human. Research using this animal model will permit experimental studies on the long-term consequences of disc displacement and controlled studies of surgical and nonsurgical procedures to repair joints, reduce pain, and preserve joint function.

Investigators have identified a potential biomarker in the synovial fluid of the TMJ that may indicate cartilage and disc degeneration in patients with osteoarthritis. These investigators believe that osteoarthritis of the TMJ is a major factor in TMD disorders.

In Fiscal Years 1993 and 1994, NIDR sponsored initiatives specifically designed to gather information about TMDs, identify gaps in the knowledge base, stimulate needed research, and educate practitioners about treatments. In addition, the NIDR-supported National Oral Health Information Clearinghouse (NOHIC) devised a package of information about TMDs for patients and practitioners. In its first year NOHIC received 4,400 inquiries, of which 1.202 requested information about TMDs. As a result, 20,000 TMD brochures and 1,300 TMD information packets have been distributed. The Institute is also planning a technology assessment conference on TMD management for the spring of 1996.

ORWH has contributed supplemented funding to three NIDR-supported TMD projects: (1) Evaluation of TMD Criteria, Fiscal Year 1993; (2) International Workshop on the TMDs and Related Pain Conditions, Fiscal Year 1994; and (3) Interagency Chronic Pain Task Force Report to Congress, Fiscal Year 1994.

#### Bone Research

Since its inception, NIDR has fostered an active bone research program with emphasis on bone biology and clinical problems, such as osteoporosis.

#### Osteoporosis

Osteoporosis is characterized by a loss of bone mass that places patients at risk for spontaneous bone fractures. As a major public health problem, it affects an estimated 20 million older Americans in a female to male ratio of 4:1. Bone is a dynamic tissue that changes continually throughout life. In healthy bone, a delicate balance between bone formation and resorption is maintained. In aging bone, that balance shifts, leaving the bone brittle and subject to fracture. NIDR research indicates that radiographs of the jaws of pre- and post-menopausal women can be distinguished from each other. Oral bone, therefore, may provide measurable features that are indicative of skeletal bone status. NIDR supports 34 basic and clinical osteoporosis research projects through its intramural and extramural programs.

#### Bone Sialoprotein

One of the most important discoveries from the NIDR Bone Research Branch (BRB) is the isolation and characterization of bone sialoprotein, a bone matrix protein. Bone sialprotein is tightly linked with bone cell maturation and matrix mineralization and, as such, serves as a potential biochemical marker for the evaluation of bone formation. In addition, BRB research collaborators found that bone sialprotein is expressed not only in cells forming mineralized matrix within bones and teeth, but also in certain pathologies characterized by extra bony calcification, as in atherosclerotic plaques of the aorta and breast tumors.

ORWH funded efforts to expand NIDR-supported basic research into the process of biomineralization essential to the development of therapies for skeletal disorders, such as osteoporosis and osteopetrosis.

Hard Tissues Disorders Club/Bone Clinic Under the leadership of BRB, an NIH Hard Tissues Disorders Club was formed, composed of clinical researchers from NIDR, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute on Aging (NIA) who wish to foster interinstitute collaborations. These collaborations will facilitate the development of diagnostic and treatment protocols for the new Bone Clinic in the NIH Clinical Center.

In its first clinical protocol, BRB investigators are obtaining bone marrow stromal cells from normal volunteers and growing them in vitro. The cell population contains precursors for bone, cartilage, fat, and supporting stroma. Biochemical analysis is beginning to characterize the differences that exist between these stem cells so that methodologies can be devised to sort the cells for use in tissue repair. Techniques are now in place to obtain bone formation when human stromal cells are implanted in mice lacking an immune system (so the cells will not be rejected). The next step will be to identify patient populations who might benefit from autologous transplants (e.g., those who have failed dental or orthopaedic implants, those with damaged hips lacking blood supply, and those with large traumatic bony defects).

#### Initiatives

#### Requests for Applications (RFA) and Requests for Proposals (RFP)

- The Institute issued an RFA with NIAMS for support of research on oral bone loss and osteoporosis in Fiscal Year 1993.
- In Fiscal Year 1994, NIDR issued an RFP to conduct an investigation of (oral hard tissue status in relation to skeletal bone mineral density measures and osteoporosis).
   Proposals are currently under review.
- In July 1993, an RFP was issued to assess clinical and psychosocial outcomes of TMJ implant/surgery through focus groups with patients and clinicians.
- In April 1994, NIDR issued an RFP on molecular biologic TMJ surgery outcomes. The closing date is January 1995.

#### Conferences and Workshops

- In April 1994, the Institute co-sponsored (NIAMS, ORWH, AHCPH, and the Food and Drug Administration [FDA]) the International Workshop on the TMDs and Related Pain Conditions. The workshop presented available information of TMDs and identified major research needs. Proceedings will be published and distributed by the International Association for the Study of Pain Press (in press).
- In September 1994, the Institute co-sponsored (NIAMS, ORWH, and FDA) a workshop on TMJ alloplastic implants and local and systemic responses: observations and research needs as a follow-up to the international workshop. The workshop aims were to (1) evaluate observations of adverse effects associated with TMJ alloplastic implants; (2) identify gaps in knowledge, (3) identify opportunities for multisite study protocols, and (4) develop a list of research needs and priorities.
- In January 1994, NIDR co-sponsored a Trans-NIH Biobehavioral Pain Research Workshop.
- In March 1994, NIDR sponsored a workshop on the advances in the understanding of chronic pain and temporomandibular

disorders at the American Association of Dental Research Scientific Frontiers in Clinical Dentistry meeting.

#### NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports basic and clinical research on diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Within NIDDK's research mission, diseases and health risks that primarily affect women include adult-onset diabetes; gestational diabetes; obesity (especially in minority populations); eating disorders—anorexia nervosa and bulimia; gastric polyposis; osteoporosis; thyroid diseases, including Graves disease, goiter, and hypothyroidism; hyperparathyroidism; gallstones; primary biliary cirrhosis; interstitial cystitis; urinary tract infections; analgesic cystitis; urinary tract infections; analgesic nephropathy; urinary incontinence; and lupus nephropathy (the kidney disease of systemic lupus erythematosus).

NIDDK supports research directed to chronic diseases of special relevance to women's health. NIDDK has a firm commitment to increasing understanding of disease processes that pose special problems for women and to developing means to treat such diseases. Research supported by NIDDK, which involves both women's and men's health, involves nutrition research as it relates to coronary artery disease, hypertension, cancer, and deficiency anemias, including iron-deficiency anemia. NIDDK has been one of five NIH institutes supporting the Postmenopausal Estrogen/Progestin Interventions (PEPI) study: a blinded, placebocontrolled clinical trial of estrogen/progestin combinations in postmenopausal women.

#### Accomplishments

#### **Breast Cancer**

Breast cancer research funded by NIDDK focuses on hormonal regulation of cellular growth and function by both steroid hormones and growth factors. Steroid hormones and growth factors regulate differentiation, growth, and developmental maturation of most normal tissues; changes in the hormonal environment

can modulate the risk of breast cancer and progression of some breast tumors. Estrogen can stimulate breast cancer growth by direct interaction with estrogen receptor-positive breast cancer cells. NIDDK grantees are developing affinity labeling agents and fluorescent ligands as molecular probes for estrogen receptors, which may apply the powerful techniques of time resolution in receptor assays and microscopic imaging, resulting in diagnostic and prognostic implications.

Progesterone, a steroid hormone that influences breast tissue, may continue its influence after transformation of breast tissue to a malignantistate. Interaction of progesterone with its receptor may arrest the growth of some breast cancers. While the precise mechanism of progesterone action is unknown, mediation by progesterone receptors does effect hormone actions. NIDDK grantees are examining progesterone receptor regulation by posttranslational modification via phosphorylation. Another group of investigators is studying a molecular chaparone mechanism involved in the assembly of progesterone-progesterone receptor complexes.

NIDDK-supported research on antihormone agents is beginning to provide therapeutic agents, which can be used as part of a larger approach to combat both breast and gynecologic cancers. This research has been facilitated by an increased understanding of the structure and function of hormone receptors.

The role of alterations in the protein, cyclin D1, which is found in breast cancers, has been studied using molecular genetics in a transgenic mouse that was developed specifically to over-express the PRAD1/cyclin D1 protein in breast epithelial cells. Nearly all of the offspring of the founder mice subsequently developed breast lesions that went on to breast cancer while mice without the transgene did not. It is apparent that the overexpressing of this protein disrupts normal growth regulation in breast tissue to a degree resulting in tumor formation. These findings may shed light on overall tumorigenesis, especially that of endocrine neoplasms of which thyroid tumors are most frequently occurring.

NIDDK supports research on the active site of the enzyme involved in estrogen production. The enzyme aromatase, which is involved in ovarian production of estrogen, is being studied because knowledge of the chemistry of its enzymatic "pocket" is critical in the further design and development of more effective and

potent agents for the control of estrogenic processes and for the treatment of advanced estrogen-dependent breast cancer.

The role of growth factors in normal cell growth, cellular transformation to tumors, and tumor spread and invasion of tissues (metastasis) has become an increasingly important focus of research by NIDDK investigators. Certain growth factor receptors have significant similarity (homology) with cellular proto-oncogenes and/or viral oncogenes. Proto-oncogenes are genes for proteins that have normal functions in cells, but which have homology to viral transformation genes known as oncogenes. Cellular transformation can occur with inappropriate expression or function of these proto-oncogenes. Mutations in the genes for growth factor receptors can result in permanent activation of these receptors even in the absence of growth factors, so cells receive an inappropriate signal to grow. Inappropriate production and release of other growth factors occur and stimulate continued expansion of the tumor with new growth of blood vessels to nurture the tumor

The role of the steroid hormone vitamin D in regulating cell proliferation is being studied by NIDDK grantees and intramural scientists who are focusing on studying various aspects of both the hormone and its cell receptor. The receptors for all steroid hormones belong to a single "superfamily" of related receptors, with similarities in structure and mechanism of action. Since breast tissue is very sensitive to steroid hormones, information gained in these studies will advance knowledge of steroid hormone action as a whole.

NIDDK's intramural research program has ongoing studies of the structure and function of certain cellular growth factors, potentially applicable to breast cancer treatment. Breast tissue cells transformed into tumor cells produce and secrete other growth factors, such as transforming-growth factor beta (TGF-b). Synthesis and excretion of TGF-b may be controlled by estrogen in hormone-dependent tumors. NIDDK scientists recently determined the three-dimensional structure of TGF-b2 (one of 18 members of the TGF-b superfamily) that may facilitate structure-based design of new therapeutic drugs.

NIDDK's nutritional research focused on the metabolism of nutrient anti-oxidants (e.g., beta carotene, vitamin D, and vitamin E), some of which may be associated with reduced risk of breast cancer, includes epidemiological, clinical, and animal studies. The metabolism and function of zinc and selenium, co-factors of anti-oxidant enzymes, which may directly prevent the development of breast cancer, are under study.

#### Osteoporosis

Osteoporosis disproportionately affects women and is a major cause of the 1.3 million bone fractures each year. It affects one-third to one-half of postmenopausal women and nearly half of people over age 75. The direct medical costs of osteoporosis in the United States reached an estimated \$10 billion in 1988, excluding the costs of family care and lost productivity for care givers. The direct medical costs of osteoporosis will rise as the proportion of older persons in the population rises.

NIDDK-supported investigators have shown that high-intensity strength exercise training improves bone density. These studies were undertaken in postmenopausal women who had not engaged in a regular exercise program and had not taken estrogen or other medications known to affect bone for at least 12 months. High-intensity exercises known to affect major muscle groups attached to the bones of interest were undertaken at least twice a week.

Osteoclasts, which have primary responsibility for bone resorption, are recruited by hormones, growth factors, and/or cytokines to the surface of bone and modulate bone resorption. Osteoclasts, a normal component of bone remodeling, when uncontrolled can result in excessive bone resorption (osteoporosis) or no bone resorption (osteopetrosis). Recently, a proto-oncogene was found to be an essential component of bone resorption. This tyrosine kinase encoding gene has been linked to signal transduction through growth factor receptors. Its absence does not affect the numbers of osteoclasts in bone, but, rather, results in the failure of the osteoclast to respond to hormonal signals, resulting in development of osteopetrosis. This exciting finding, developed by the use of novel transgenic mouse models, now fills in a large gap in our knowledge of the mechanism of osteoclast response to hormonal stimulation.

Bone cells respond to estrogen, a hormone that protects against bone resorption. Menopause, with its decrease in estrogen levels, places women at increased risk for development of osteoporosis and related bone fractures. In postmenopausal women, estrogen replacement is effective in slowing/preventing osteoporosis.

NIDDK, along with four other NIH institutes, participates in the PEPI clinical trial initiated by the National Heart, Lung, and Blood Institute. PEPI is comprehensively evaluating the effects of postmenopausal estrogen replacement on lipids, blood coagulation, glucose metabolism, blood pressure, and bone mass; PEPI also compares the risks and benefits of several approaches to estrogen replacement to prevent osteoporosis. NIDDK also participates in the NIH-wide Women's Health Initiative, which will study the use of estrogen, calcium, and vitamin D in the prevention of osteoporosis.

NIDDK grantees identified a number of growth factors, cytokines, which may have a role in regulation of bone metabolism. Boneactive cytokines may act collectively to regulate the processes associated with bone metabolism. Physiological effects of cytokines at the cellular level are being studied in model systems.

#### Diabetes Mellitus

NIDDK, which has lead responsibility for diabetes mellitus at NIH, supports research into the spectrum of basic and clinical research related to diabetes and its complications. Diabetes is the sixth leading cause of death from disease in the United States, the third leading cause of death from diseases in African-American women, and the seventh leading cause in African-American men. An estimated 13 to 14 million Americans have diabetes. Medical care and lost productivity cost the United States \$20 to \$25 billion annually. Diabetes mellitus is the leading cause of new adult blindness, kidney failure, and nontraumatic lower extremity amputations; it is a major risk factor for stroke, heart attack, and premature death.

Noninsulin-dependent diabetes mellitus (NIDDM), or adult-onset diabetes, is the most common type of diabetes. While the prevalence of NIDDM today is 33 percent higher in African Americans than in Caucasians, it is twice as high in African-American women as in Caucasian women. Hispanics also have an incidence of diabetes disproportionate to their representation in the U.S. population. NIDDM and its complications are an increasing health problem for certain American-Indian populations. Sixtyeight percent of Pima Indian women ages 55 to 64 have NIDDM, and overall rates of NIDDM are often two to five times higher among American Indians than among other U.S. populations. Native Hawaiians also have a high incidence of diabetes.

Thirty to forty percent of diabetic patients develop kidney disease of diabetes mellitus (KDDM). More than 30 percent of new patients entering the End-Stage Renal Disease (ESRD) Medicare Program have KDDM. It is estimated that within the next decade, KDDM will be responsible for more than half of all ESRD Medicare patients. KDDM disproportionately affects African Americans and American Indians. In addition, urinary tract infections and urinary bladder dysfunctions (including urinary incontinence and urinary retention) occur in a significant percentage of diabetics. These disorders occur at a much higher incidence than in the general population and at a much younger age of onset.

The Diabetes Control and Complications Trial followed 1,441 subjects in 29 clinical centers in the United States and Canada for a mean of 6.5 years. This study convincingly established the benefits and risks of intensive therapy of insulin dependent diabetes mellitus (IDDM). Intensive therapy delayed the onset and slowed the progression of the composite of major complications of IDDM. However, there was a significant increased risk for severe hypoglycemia.

NIDDK researchers analyzed dietary data from diabetic female participants in the Nurses Health Study to determine whether their diets met American Diabetes Association dietary recommendations. The cohort of 121,700 registered women nurses studied were followed for 17 years. Women with IDDM and NIDDM consumed less energy from carbohydrates and more energy from protein and fat than did the control women. The results show that these diabetic women did not consume the high-carbohydrate, low-fat diets recommended by the American Diabetes Association over the past decade.

Psychosocial correlates of glycemic control of IDDM patients were examined in patients 18 years of age and older. Gender was found to be related to self-care activities with women reporting more self-care behavior than men.

Individuals with NIDDM are unable to regulate blood glucose levels even though they may produce massive quantities of insulin. NIDDK-supported researchers have uncovered a wide variety of biological defects that may lead to this condition. Insulin normally acts on target cells by reacting with an insulin-specific receptor in the cell membrane. Binding to this receptor sets off a chain of events in the cell that leads specifically to increased transport of

glucose from the blood into the cell. Special insulin-sensitive transporter proteins have been discovered that perform this job under the control of insulin in normal cells. The significance of alteration in just one base in the DNA coding for the insulin receptor has been described by an NIDDK investigator and his collaborators in work with patients who have NIDDM. Patients with this condition can now be examined for genetic variations in the crucial regions of the insulin receptor and the insulinresponsive glucose transporter. Recent genetic studies on several physiologic components (i.e., the glucose transporter gene, the glucokinase gene, and the insulin gene promoter) that can contribute to NIDDM have produced data about the causes of this disease, which may help in identification of persons at risk. Other recent work has increased understanding of the insulin-producing (beta) cell response to glucose and the significance of diet, weight reduction, and oral agents in the optimization of beta cell responsiveness to glucose

#### Gestational Diabetes

Fetal mortality and perinatal mortality are estimated to increase three to eight times among the pregnancies of diabetic mothers. Congenital malformations are more common and macrosomia is seen at least twice as often. As more women with IDDM reach childbearing age in good health, the number of diabetic pregnancies has increased. More women, especially among minority populations, are developing NIDDM at younger childbearing ages.

Gestational diabetes is caused by glucose intolerance that develops during 1 to 2 percent of pregnancies. Of the women who have gestational diabetes, about 25 percent will develop either IDDM or NIDDM. An NIDDK analysis of data from the second National Health and Nutritional Survey (NHANES II) suggests that gestational diabetes may be a "silent" condition that actually precedes pregnancy but is only detected during the routine testing that accompanies prenatal care. Gestational diabetes increases not only the risk of future diabetes in affected mothers but also the risk of health problems in newborns. While maternal diabetes has well-documented adverse effects on other outcomes of pregnancy, the underlying pathophysiologic processes that lead to increased perinatal mortality, prematurity, congenital malformations, and macrosomia have not been delineated

## Obesity

Obesity is a major risk factor for diabetes, cardiovascular disease, and stroke and has been implicated in certain forms of cancer. Repeated dieting to control obesity may contribute to osteoporosis, if bone loss occurs. One-quarter to one-third of adults in the United States are considered overweight. The prevalence of morbid obesity has increased during the last two decades. Its prevalence is disproportionately high in particular populations, especially women, the poor, and ethnic groups, including African Americans, Mexican Americans, American Indians, Alaska Natives, Hawaiians, and Japanese Americans. By U.S. Department of Agriculture (USDA) guidelines, 51 percent of African-American women and 49 percent of Mexican-American women are overweight. While both genetic and environmental factors are involved in causing obesity, decades of research on the causes of overweight have yet to reveal a complete understanding of the biological, cultural, socioeconomic, and behavioral determinants and interrelationships of this condition.

The relationship of rodent and human obesity genes is of major relevance to human obesity. The recent identification of a mouse obesity gene is a major advance. Experiments are underway to determine the role that mouse genes may play in obesity of Caucasians, African Americans, American Indians, and Hispanics.

With the Office of Research on Minority Health, (ORMH) NIDDK is jointly sponsoring the first major controlled clinical trial of obesity treatment in African-American women and is monitoring the impact of weight loss as well as changes in risk factors for comorbid conditions. Because obese Mexican-American women with a history of gestational diabetes mellitus (GDM) are at high risk for NIDDM, an ORMH/NIDDK joint 5-year clinical study will identify early metabolic defects in Mexican-American women with prior GDM.

Investigators at an NIDDK-supported Obesity Research Center are continuing studies of the underlying mechanisms of obesity, especially possible defects in thermogenesis in African-American women in comparison to Caucasian women, and differences in fat cell morphology and/or fat cell metabolism between African-American and Caucasian women. Such differences, if they exist, may predispose to the development of obesity and the resulting complications of obesity in African-American women.

## Obesity and Diabetes

Obesity is the most prominent risk factor in the development of NIDDM. Approximately one-half of NIDDM is believed to be attributable to obesity. Diabetes mellitus, a major cause of mortality and morbidity in women, affects approximately one in seven women over age 45. Both obesity and NIDDM are more prevalent among minority groups. Because 85 to 90 percent of diabetics have NIDDM, nearly one-half of all diabetes might be preventable through control of obesity. A recently completed NIDDK-supported study demonstrated that insulin resistance, the cardinal sign of NIDDM, develops at a subclinical level with increasing body weight only when the weight increases beyond 120 percent of normal, and that below this threshold there is an apparent causal relationship between obesity and diabetes.

The higher prevalence of NIDDM in minority populations has been correlated with their high rates of obesity. Among people with NIDDM, 82 percent of adult African-American women are obese as compared to 62 percent of non-Hispanic Caucasian women. NIDDK grantees analyzed data from national health surveys, and found that African Americans of normal body weight have no greater risk for diabetes than do Caucasians, but that as body weight increases the risk for diabetes increases disproportionately in African Americans. This suggests that African Americans have a higher risk of NIDDM not only because of their higher prevalence of obesity, but also because the degree of their obesity carries proportionately greater risk. The prevention and control of obesity, particularly in minority populations, is clearly of major importance in the prevention and treatment of NIDDM.

In addition, pregnant, obese, diabetic women often deliver babies who are larger and more likely to experience hypoglycemia during their first 72 hours of postnatal life compared to babies of lean diabetic and nondiabetic women. Other adverse effects on the fetus correlate directly with the severity of maternal disease.

#### Thyroid Disease

Diseases of the thyroid, in particular autoimmune disorders such as Graves disease and Hashimoto thyroiditis, predominantly affect women. Graves disease is the most common cause of hyperthyroidism, and occurs four times more frequently in women than in men.

Although effective therapy is available for the thyroid component of Graves disease, current therapies are not ideal since removal or ablation of the thyroid can result in lifelong hypothyroidism requiring hormone replacement therapy and use of antithyroid agents is often followed by recurrence of disease. New therapeutic modalities are particularly needed for the eye component of the disease.

Hypothyroidism, often due to autoimmune thyroid disease, predominantly affects women, with 3 to 4 percent of middle-age and older women affected. Thyroid hormone is one of the most commonly prescribed drugs in women, and NIDDK grantees recently developed a blood test that will allow physicians to optimize the dose of thyroid hormone. Other common thyroid diseases in women include nodules and goiter, as well as thyroid dysfunction associated with pregnancy and the postpartum period. Progress has been made in understanding thyroid hormone action. Linkage between nutritional disorders and the refractoriness to thyroid hormone action can be attributed to deficiency of the trace element, selenium. The ability of cells to respond to thyroid hormone depends on the presence of intact, full functional receptors. Mutations in specific functional domains of the receptor may cause generalized resistance to thyroid hormone. Important structural studies can help to define the complex interactions that occur between thyroid hormones and binding proteins and/or receptors in the intact organism and may perhaps be relevant to developing strategies for drug design in the treatment of thyroid disease. Finally, the mechanism by which autoantibodies stimulate thyroid cell function has important implications for understanding and treating Graves disease.

#### Gallstones

Ten to 15 percent of adult Americans (about 20 million people) have gallstones. Populations known to be at higher risk for the development of gallstone disease include American Indians (especially the Pimas) and Hispanic populations (especially Mexican Americans). African Americans have a lower prevalence of gallstone disease than Caucasians. In all populations, women have a higher prevalence than men. Obesity and rapid weight loss are risk factors for gallstone disease. The incidence of gallstones among women who lost weight rapidly approaches 25 percent, while a 10-percent recurrence rate per year prevails among persons

who have gallstones successfully dissolved by bile acid therapy alone or in combination with extracorporeal shock-wave lithotripsy. These two groups of patients potentially represent 50,000 to 100,000 new cases of gallstones per year in the United States.

Patients with high rates of symptomatic gallstones require treatment, and removal of the gallbladder is the conventional therapy for most patients with symptomatic gallstone disease because an intact gallbladder invites recurrence of gallstones in one-half of treated individuals. Half a million of these procedures are performed yearly in the United States at an annual estimated cost of \$5 billion (not including cost of lost work time).

Published NIDDK-supported studies have clarified the importance of dietary patterns and weight loss on the risk of developing gallstones. In a study of 248 obese subjects treated with 16 weeks of a very low-calorie diet at Cedars Sinai Hospital in Los Angeles, 11 percent developed gallstones Risk factors for the development of gallstones were degree of obesity, rate of weight loss, and blood triglycende levels. The investigators found weight loss to be associated with an increase in biliary prostaglandins and glycoproteins, which are thought to be important for gallstone nucleation. Another group of investigators found that the development of gallstones among persons who lost weight rapidly was accompanied by increased mucin (primarily composed of glycoproteins) and calcium in the gallbladder Calcium salts also have been associated with gallstone nucleation. One aspect of gallstone development during weight loss may be an increase in nucleating factors.

Follow-up of 90,000 nurses from various areas in the country has demonstrated that women who lost at least 22 pounds during a 2-year period had twice the risk of developing clinically recognized gallstones as women whose weight remained stable. The greatest risk was among the most obese women, but some increased risk was found regardless of the degree of preexisting obesity. A third study that followed a nationally representative sample of women for 10 years found that women who tended to have a long overnight fast (14 hours or more) had an increased risk of being hospitalized for gallstone disease during the followup period. Women who reported being on a diet had a higher risk of subsequent hospitalization for gallstones than women who did not diet.

Despite the rapid growth in recent years of nonsurgical techniques by which cholesterol gallstones can be dissolved or fragmented. current research centers on understanding the formation of gallstones and intervening in that process. The focus of recent work has shifted from the physical chemistry of the bile in the formation of gallstones to the physiological functions of the gallbladder. Work continues on special factors present in the bile, such as nucleating and antinucleating proteins, and these need to be evaluated along with factors that influence gallbladder functions: motility, secretion, and absorption. Preliminary data from an NIDDK-sponsored study suggest that both ursodeoxycholic acid (UDCA) and aspirin may prevent the occurrence of gallstones among women undergoing weight reduction diets.

## Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC), an autoimmune disease characterized by a gradual inflammatory destruction of the small bile ducts of the liver, is a life-threatening chronic liver disease that tends to affect women in their thirties and forties. PBC leads to progressive liver injury with resultant cirrhosis of the liver and death from liver failure, 2 to 10 years after onset of symptoms. PBC is the most common indication for liver transplantation in adults. An estimated 200 patients with PBC have liver transplants annually. If a medical treatment could be found to delay or prevent this disease, a large cost savings could be realized, as could the dilemmas posed by the scarce resource, donated human livers.

NIDDK has supported intramural and extramural randomized trials enlisting small numbers of patients with PBC. Positive effects of the medications colchicine, chlorambucil, cyclosporine, UDCA, and methotrexate on liver function tests, tissue structure, and mortality have been reported. NIDDK grantees at the Mayo Clinic have developed a mathematical model for accurately predicting survival of individuals with PBC using only noninvasive measurements. The Mayo risk factor model improves decisionmaking related to the appropriate timing for liver transplantation in patients with PBC and may provide a staging method of disease progression to assess efficacy in clinical trials.

In other NIDDK-supported research, it was shown that autoantibodies from sera of patients with PBC react with a complex of enzymes that is important in the cell's metabolism, a finding that led to development of better diagnostic assays to detect the disease. Investigators have also recently induced an autoimmune-like disease in mice with severe combined immunodeficiency. This animal model should enable researchers to examine the precise features of the disease and to test drugs that may prevent or delay its progression. Although immune substances characteristic of PBC have been identified, their relevance to the origin and development of this disease still must be clarified. Further research will also focus on development of pharmacologic mediators of PBC.

## End-Stage Renal Disease

Diabetes mellitus is the most common cause of end-stage renal disease (ESRD). It is one of the few conditions causing ESRD with a female predominance overall and particularly among African Americans. From 1987 through 1989, the incidence, per million population, of ESRD among African Americans with diabetes was 115.6 among males and 143.2 among females. NIDDK supports a substantial research portfolio to investigate the diagnosis, treatment, and prevention of the kidney disease of diabetes mellitus.

Several avenues of research are approaching the problem of how kidney disease of diabetes mellitus develops and how it might be arrested before serious renal damage occurs. One area under investigation is the effect of the altered body chemistry that occurs when the blood sugar level remains too high. Research has suggested that advanced glycosylation end products (AGEs), which result from elevated blood sugar, may lead to kidney scarring by beginning a process that results in increased connective tissue formation. Indeed, in an in vitro model mimicking the effects of the AGEs. enhanced formation of connective tissue components did occur. When the drug aminoguanidine was used to inhibit the activity of AGEs, the effect of the AGEs was reversed. This finding, along with results from other fundamental research, helps to identify factors at the molecular and cellular levels that contribute to the altered kidney processes typical of KDDM. Findings to date suggest the possibility of preventing KDDM by drug or gene therapy to reverse specific biochemical changes caused by diabetes.

NIDDK supports several clinical and epidemiologic studies focusing on understanding, treating, and preventing KDDM. The Diabetes

Control and Complications Trial includes studies comparing the rate of KDDM progression in insulin-dependent diabetes mellitus patients. In a multicenter clinical study under way in collaboration with the Souibb Institute for Medical Research, researchers are investigating whether a drug used to treat high blood pressure can decrease the diabetic glomerular injury and slow the decline in renal function. Findings in a comprehensive epidemiologic and natural history study of diabetic renal disease in the Pima Indian population are being used to develop clinical studies of KDDM. Another project, begun in 1991, is determining whether familial clustering of kidney diseases has an identifiable mode of inheritance in African Americans and if characterization of presymptomatic clinical markers is possible

## Urologic Disorders

Research into the urological disorders of women focuses on the pathogenesis and prevention of diseases and disorders of the urinary tract, which are major health problems for women of all ages. Urinary tract infections and urinary incontinence cause a significant number of physician visits and hospitalizations. The pathogenesis of many of these disorders remains poorly understood, and preventive and curative methods have yet to be developed. Treatment is often improper due to lack of adequate diagnostic evaluation or due to patient self-treatment without physician input. Specific areas of women's urological disorders requiring attention include urinary incontinence and other bladder dysfunctions, urinary tract infections including cystitis and pyelonephritis, interstitial cystitis and other chronic inflammatory disorders of the bladder and urethra, and the bladder dysfunction of diabetes mellitus

Factors disturbing neurological and muscular interactions involved in normal bladder function can result in identical bladder dysfunctions even with significantly diverse etiologies.

When the bladder outlet is chronically obstructed, forcing the bladder muscle to contract against a strong resistance, the bladder eventually decompensates and loses its coordinated functions of storing and emptying. Diabetes mellitus has an identical, long-term effect on the bladder, resulting in decompensation and loss of its storing and emptying functions.

Recent studies have provided significant insights into the cellular and molecular mechanisms that result when bladder dysfunction occurs secondarily, either to bladder outlet obstruction or to diabetes. Either diabetes or chronic obstruction produces disturbances in the metabolism within adult bladder muscle cells and causes irreversible changes that affect both protein synthesis and muscular contractility. These changes lead to the abnormal bladder function associated with these conditions. These studies demonstrate that there is an inherent plasticity in the bladder and if metabolic changes are detected and corrected early, long-term damage might be prevented

### Interstitial Cystitis

Interstitial cystitis (IC) is an extremely painful and debilitating disease of the bladder that predominantly affects women. Because it is difficult to diagnose, the precise prevalence of IC has been difficult to determine. The major pathologic signs of IC are scarring and stiffening of the bladder wall and ulcers or cracks in the lining of the bladder. The major symptoms are a frequent, urgent need to urinate and intermittent or chronic pain. In severely affected patients, these symptoms may diminish the patient's quality of life by restricting professional, social, and sexual activities. The cause of IC is unknown and no effective treatment has yet been identified

Because not all people diagnosed with IC have all of the symptoms, it is a difficult disorder to diagnose, treat and study. To address these issues, NIDDK has worked with researchers, clinicians, and the IC community to develop a preliminary set of uniform diagnostic criteria that will facilitate research on this disease. Researchers are endeavoring to identify and characterize the pathogenetic mechanisms that identify, amplify, and maintain the pathological bladder dysfunction of interstitial cystitis and to explore therapeutic modalities. Diligent efforts are being made by NIDDK to establish a strong research base for this disease so that its biological mechanisms and predisposing factors can be pinpointed. Concerted efforts in epidemiology, pathophysiology, bladder neurophysiology, and molecular biology should lead to accelerated progress in understanding and treating this disease

NIDDK-supported investigators have undertaken a series of elegant experiments to define the neurophysiology of the bladder and its modification by disease. They demonstrated a neural network of the bladder and showed that inflammatory or painful conditions in the lower

urinary tract can induce a chronic bladder hyperactivity by three distinct mechanisms: (1) the action of inflammatory mediators on bladder smooth muscle, which increases muscle excitability; (2) sensitization of bladder afferent receptors; and (3) enhancement of central reflex mechanisms.

Other investigators studied expression of a specific glycoprotein (GP1) of the surface mucin of the bladder in biopsy specimens from IC patients and from controls. While the controls had significant amounts of GP1, 35 percent of patients had no GP1 expression and 61 percent of patients had minimal expression as compared to controls.

The NIDDK Interstitial Cystitis Database was established in 1989 as a pilot study and was expanded to a full-scale database in 1991. The clinical centers participating in the database project will recruit and follow patients with IC, collect demographic and symptom information, and collect patient specimens, including bladder biopsy material under standardized protocol. The data collected will be used in the development of epidemiologic and other studies to gain insight into the pathogenesis of IC and effective means of treating it.

## Urinary Tract Infections and Urinary Incontinence

Infections of the urinary tract (UTI) are common; only respiratory infections occur more often. Each year, UTIs account for about 8 million physician visits and are responsible for approximately 25 percent of the absenteeism among women workers. Women are especially prone to UTIs for reasons that are poorly understood. One woman in five develops a UTI during her lifetime. Urinary incontinence affects at least 10 million adult Americans, including approximately 15 to 30 percent of community-dwelling older people and at least one-half of all nursing home residents. In fact, urinary incontinence is responsible for nursing home referrals. Prevalence rates are twice as high in women as in men. The monetary costs of managing urinary incontinence are conservatively estimated at \$10.3 billion annually. Risk factors include UTIs, menopause, and lack of postpartum exercise.

NIDDK grantees recently demonstrated that women with a history of recurrent UTIs have a significantly different frequency pattern of blood groups in comparison with a control group of women. These inherited blood groups

are important factors in determining the complex carbohydrate membrane structure of epithelial cells in both the bladder and vagina (to which infection-causing bacteria adhere). These findings strongly suggest that there is an inherited factor associated with the risk of acquiring a UTI. Another team of investigators has demonstrated in experimental models that local immunization of the vaginal mucosa against the bacterium E. coli resulted in more rapid resolution of experimentally induced bladder infections. However, when the immunization was intensified, there was a lessened protective response. These findings are important steps in developing an intervention to prevent UTIs in susceptible persons.

## NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to reduce the burden of environmentally associated diseases and dysfunctions by defining (1) how environmental exposures affect our health, (2) how individuals differ in their susceptibility to these effects, and (3) how these susceptibilities change over time. A number of diseases that predominate in women appear to have an environmental component, including breast cancer, endometrial cancer, osteoporosis, and autoimmune diseases. NIEHS has a long tradition of supporting research related to women's health, and this past year has brought many significant achievements that will advance our understanding in this area.

## Accomplishments

#### **Breast Cancer**

Breast cancer continues to be a major health problem for women. The death rate from this disease increased by a disturbing 24 percent between 1979 and 1986. Today one in nine women will develop breast cancer. Abundant epidemiologic and experimental data support the probable role of environmental factors and chemical carcinogens in the etiology of breast cancer. Currently, NIEHS intramural and extramural scientists are pursuing aspects of breast carcinogenesis, including studies of the breast cancer susceptibility gene (BRCA1), studies on individual differences in carcinogenetabolizing enzymes and breast cancer suscep-

tibility, studies to define the steroid hormone growth-regulatory pathways in the mammary gland, and studies exploring the role of fat-soluble pesticides in breast cancer development.

NIEHS scientists, working with researchers in Utah, have successfully isolated the breast cancer gene BRCA1. BRCA1 is thought to account for 5 percent of breast cancer cases overall and for 25 percent of early-onset (women under age 30) breast cancer cases. The discovery of the exact location of this gene brings us significantly closer to understanding the origins of developing this devastating disease. NIEHS scientists plan to study the ability of different environmental agents to mutate this gene, which is critical to the development of many cases of breast cancer.

Ongoing research supported by NIEHS is using estrogenic compounds as probes to study the estrogen receptor in target tissues and their modulatory effects upon the subsequent genetic expression. The evidence suggests that some mutations resulting in slight alterations in the protein configuration of the estrogen receptor molecule may be important in the etiology of certain types of breast cancer. These mutations may be a direct consequence of environmental toxin exposure.

Exposure to electric and magnetic fields has been suggested as a possible risk factor for breast cancer development. NIEHS has an increasing portfolio on biological effects arising from exposure to electric and magnetic fields and much of this work is devoted to testing the hypothesis linking breast cancer and exposure to electric and magnetic fields. This research portfolio has both basic biology and clinical components. In one study the levels of the hormone melatonin are being measured in volunteers with and without exposures to electric and magnetic fields. This hormone has been suggested to have a role in development of breast cancer; in animal studies, electric and magnetic fields are reported to reduce nocturnal production of melatonin.

Six awards were made by NIEHS and the National Cancer Institute (NCI) in the Northeastern United States to focus attention on the environmental risk factors for breast cancer in this high incidence area. These studies are evaluating blood levels of organochlorine pesticides in women with breast cancer and healthy controls. Other occupational and environmental risk factors under assessment include exposure to electromagnetic radiation,

occupational carcinogens, smoking, and medical and other sources of X-rays. NIEHS also funds three population studies of pesticides and breast cancer in urban and rural areas, in majority and minority populations

NIEHS is collaborating with NCI on The Long Island Breast Cancer Study Project, which is a large case-control study of environmental risk factors for breast cancer in Nassau and Suffolk Counties in New York. Home measurements of electromagnetic field radiation, house dust, soil and water samples will be analyzed. Blood will be collected to analyze exposure to organochlorine pesticides, and relevant biological markers of exposure and genetic susceptibility. Urine will be analyzed for estrogen metabolites.

NIEHS funded six experimental grants dealing with the mechanism of action of those environmental agents that have been thought to contribute to the risk of breast cancer. NIEHS participated with NCI in funding four cancer centers to develop scientific programs focusing on the role of the environment. These programs include research in basic science, epidemiology, and clinical research.

#### Ovarian Cancer

The BRCA1 gene is associated with a higher risk of ovarian cancer, as well as breast cancer. An in situ hybridization procedure is being developed to detect the BRCA1 messenger RNA and to examine how its expression affects ovarian tumor development. Nitrofurazone-induced ovarian tumors are being examined.

#### **Endometrial Cancer**

Although endometrial cancer is the most commonly diagnosed gynecologic malignancy in the United States (40,000 new cases annually), few published data exist concerning the molecular basis of this cancer. There is evidence for the existence of distinct forms of endometrial cancer-an estrogen-dependent form and another form with no known association with estrogen or estrogen imbalances. Hypothetically these two distinct forms would indicate separate molecular events leading to their development. NIEHS intramural scientists have already shown a distinct pattern of mutations in the development of endometrial cancer (early ras mutagen followed by mutations in tumorsuppressor genes p53 and DCC). They have also shown that DCC is probably involved with cellular differentiation. Human uterine

tissues from women with either endometrial cancer or endometriosis overexpress a number of cellular communication proteins, such as TGF- and other cytokines. This observation has led the lab to begin extensive allelotyping analysis of proliferative human uterine tissue to determine which cellular control mechanisms are malfunctioning.

#### Cervical Cancer

Smoking is considered to be a risk factor for a variety of anogenital diseases, such as cancer of the cervix, vagina, and vulva. Research underway during Fiscal Year 1994 focuses on determining the role of a marker of genetic susceptibility GST-M1 in the etiology of these smoking-related diseases. Other studies focus on adverse effects, including cervical cancer risks, of exposure to pesticides, mercury and nitrous oxide. These latter two exposures would be found among dentists and dental assistants, among other groups, and have already been implicated in reduced fertility.

## Osteoporosis

Osteoporosis is a significant problem for older people, especially postmenopausal women. Cadmium, lead, and possibly other heavy metals found in the environment may be significant factors in the etiology of this disease. Important questions remain regarding the competition of these heavy metals with calcium in bone deposition and reabsorption. Since the condition appears more severe in women without ovaries or ovarian activity (i.e., postmenopausal), understanding the modulatory effects of estrogens on heavy metal toxicity may contribute to our knowledge of the disease. NIEHS-supported research has shown that cadmium exposure results in an increased loss of bone mineral in ovariectomized mice. The bone loss appears to occur from a direct action of cadmium on bone, not through an indirect effect on kidney reabsorption of calcium. Cadmium has been implicated in the etiology of Itai-Itai disease (osteoporosis/osteomalacia) in postmenopausal Japanese women. Thus, cadmium exposure may be a significant factor contributing to osteoporosis in older women. Furthermore, ongoing research at NIEHS continues to probe the estrogen receptor mechanism in bone cells and to examine the role of that receptor complex in the induction of certain genes. Thus, continued efforts to study the basic physiology of bone metabolism as well as the mechanisms of heavy metal toxicity in bone

tissue should provide insight into the disease mechanisms of osteoporosis.

#### Female Hormone Function

NIEHS is conducting and supporting a variety of studies on the long-term effects of female hormone function. Menstrual records collected over the past 50 years by a group of Minnesota women are being used to study broad associations between menstruation and later disease. including breast cancer, colon cancer, cardiovascular disease, thyroid disease, and general longevity. In another study, a unique set of daily urinary hormone data is being used to understand the connections between endocrine function and menstrual patterns. Occupational exposures that impair fertility are also being investigated for their effects on more general female endocrine function. Additional studies are required to establish the crucial links between environmental toxins, women's reproductive function, and women's eventual risk of chronic disease.

# Environmental Estrogens, Including Diseases Related to Diethylstilbestrol (DES) Exposure

Diseases and other health-threatening conditions found predominantly in women are often related to hormonal imbalances. The maintenance of homeostatic conditions in many tissues—bone, liver, circulatory, ovarian, uterine, and mammary— is especially sensitive to estrogenic hormones. Osteoporosis, reproductive tissue tumors, coronary heart disease, and stroke are prevalent health problems in women that have possible correlations with too little or too much of these hormones. It is also true that many environmental substances have estrogen-like qualities and compete with the normal hormone in the modulation of cellular responsiveness with key target tissues. Thus, exposure to such environmental toxins can contribute to the dysfunction and potential pathology of the reproductive system and other hormonally dependent tissues.

Women are exposed to estrogenic compounds through a variety of endogenous and exogenous sources. Included in the latter category are the phytoestrogens, naturally occurring plant estrogens. Preliminary findings by NIEHS grantees suggest that postmenopausal women whose diets are rich in soy products, which are high in phytoestrogens, are at less risk for osteoporosis than are women whose diets are low in these phytoestrogens. There is continued emphasis through NIEHS-supported research

on trying to understand the mechanisms (bene ficial or malevolent) by which these environmental estrogens contribute to the alteration of normal reproductive physiology.

Estrogenic compounds also have powerful influences on the differentiation of certain cells during critical stages of development. In utero exposure to DES has placed those females at an increased risk for developing cervical and vaginal cancers. Concerns exist that many other environmental substances known to have estrogenic activity (e.g., some pesticides. flavonoids) may be factors in reproductive tract carcinogenesis. The most potent known estrogenic compound is DES, a synthetic estrogen given to mothers for high-risk pregnancies during the 1940s through 1960s. This drug has now been linked to the development of an otherwise extremely rare malignancy, clear cell carcinoma of the vagina, in young female offspring exposed in utero. In addition, a number of more common nonneoplastic changes in the reproductive tract of DES-exposed daughters have been identified, including vaginal adenosis, cervical ectropion, and other structural abnormalities. NIEHS has an extensive research history on DES and is currently analyzing human and animal tumors resulting from DES exposure in utero for molecular genetic alterations caused by DES. It is hoped that this work can lead to development of a molecular genetic marker for DES carcinogenicity that could be used to identify and council high-risk individuals

Study of estrogen receptor-mediated health effects, such as those arising from exposure to environmental estrogens, has been hampered by the lack of an estrogen-receptor-deficient animal model. NIEHS scientists, collaborating with researchers at the University of North Carolina at Chapel Hill, have now developed a transgenic mouse that can aid in defining the role of environmental estrogens in human diseases and dysfunctions. In this mouse an important estrogen receptor has been "knocked out," thereby allowing investigators to evaluate the mechanism of action of hormonally active xenobiotics. This mouse model will be used to study actions of estrogenic chemicals in a variety of organ systems, including the reproductive tract, skeleton, cardiovascular system, and brain.

#### Endometriosis

Endometriosis affects an estimated 10 to 15 percent of the premenopausal female population and is a leading cause of pain and infertility in

this population. Despite a vast clinical literature on this topic, the etiology of endometriosis remains obscure. Many of the risk factors for this disease, as for endometrial cancer, are related to high, prolonged, or unopposed exposure to estrogens. The bodily accumulation of environmental toxins with estrogenic potential is therefore likely to contribute to the development of endometriosis in some nary evidence supporting the hypothesis that certain molecular genetic alterations found in endometrial carcinoma, especially the type I estrogen-related tumors, may also play a role in the aberrant growth and invasion properties of endometriosis. A novel gene product of endometrial epithelial cells has also been identified, to which high levels of serum antibodies exist in some endometriosis patients.

Unusually high rates of endometriosis are found in primates exposed to the ubiquitous contaminant dioxin. Based on this observation, NIEHS conducted a pilot study of 20 women with endometriosis and 20 women without endometriosis. Levels of dioxin were measured to determine if there was an association. The pilot study did not indicate that dioxin is associated with risk of endometriosis, the negative result might be due to the small sample size. A population having much larger dioxin exposures could more readily show an association with endometriosis. At the encouragement of NIEHS scientists, health officials in Italy are incorporating endometriosis as one of their monitoring measures for a population inadvertently exposed to high levels of dioxin during an industrial accident there This study would have a greater statistical power to determine if there is a link between dioxin exposure and endometriosis in human populations

#### Uterine Fibroids

Uterine fibroids, or leiomyomas, are the most common of all tumors in women. These tumors are present in 20 to 30 percent of all women over age 30; leiomyoma is significantly more common in black women than in white women. There is a considerable body of evidence that supports the role of estrogen in the development of this tumor. Consequently, chronic exposure to those environmental toxins that exert estrogenic effects would be predicted to contribute to the development of leiomyoma. A staff epidemiologist is developing a proposal for a

comprehensive study of risk factors for uterine fibroids. This study will also address issues of detection, susceptibility, and fibroid biology. The Institute hopes to conduct this study in conjunction with a health maintenance organization so that asymptomatic women can be identified through screening.

## Infertility

The NIEHS research program on the environmental contributors of reproductive outcomes is varied. Several epidemiological studies deal with the exposure to toxic chemicals, such as PBBs, polychlorinated biphenyls (PCBs), pesticides, and industrial solvents and with outcomes related to fertility, such as spontaneous abortion, and birth outcomes, such as intrauterine growth retardation. A study of hypertension in lead-exposed women who are pregnant is also underway. Work supported on reproductive toxicology is extensive. Dietary estrogens and antiestrogens and their effects on estrogen target cell function, including uterine and breast cells. Gene expression in uterine cells is being studied in response to challenges with estrogenic pesticides. The effects of polyaromatic compounds on the placenta proteins are being studied to elucidate the mechanism of intrauterine growth retardation associated with smoking during pregnancy. The effects of cadmium on placental function is also being studied. Several grantees are studying the effects of TCDD on endometrium, cervix, and breast in laboratory animals. Biomarkers for reproductive hazards and effects are also being developed.

#### Maternal Exposure and Fetal Development

Many toxic agents are fat-soluble. When women are exposed to these compounds, they store them in body fat. Consequently, a woman's offspring can be exposed to these fat-soluble compounds, either during gestation or when nursing, since these toxins also appear in the fat of breast milk. A recent collaborative NIEHS epidemiological study demonstrated the potential of toxicity from this phenomenon. A group of Taiwanese women accidentally exposed to a class of neurotoxins, PCBs, gave birth to children with a persistent, although small (5 points), deficit in intelligence. Disturbingly, these deficits were detected both in children born near the time of exposure and in children born up to 6 years after the maternal exposure. The persistence of PCBs in the mother's body, as well as

her ability to pass these exposures on to her children during gestation and breast feeding, indicates a need to identify and counsel highrisk women.

Also targeted for emphasis are studies of how individual and gender variations affect vulnerability to the effects of environmental toxicants. New advances in the fields of genetics and molecular biology have facilitated the study of genetic variations. The Institute plans to use these techniques to explore the enhanced susceptibility of women to certain environmentally linked diseases. For example, NIEHS will do polymorphic analyses of specific receptor proteins that may correlate with increased infertility or hormone-induced tissue pathology.

#### Lupus

Women are more likely than men to develop autoimmune diseases, such as multiple sclerosis and systemic lupus erythematosus (SLE). Environmental factors are thought to play a role in these diseases. One NIEHS grantee has a model system in which mercury-exposed rats develop autoantibodies to laminin, a basement membrane protein. The antibodies formed prevent implantation in pregnant rats; similar antibodies have been found in monkeys and women who have a lot of fetal wastage. Women with SLE have higher rates of spontaneous abortion, and it is thought that their autoimmunity is a contributing factor. This researcher is trying to establish if the autoantibodies in women with SLE are similar to the autoantibodies to laminin in the mercury-exposed rats and, if so, will examine further the environmental factors contributing to the development of autoimmunity.

## Toxicological Research and Testing— Gender Differences

Males and females can differ, sometimes significantly, in their responses to environmental agents. NIEHS, which under the auspices of the National Toxicology Program (NTP) operates the largest federal testing program, has always ensured that gender differences are accounted for in these studies. As a matter of policy, the long-term NIEHS/NTP studies are done in both sexes of rats and mice. Health endpoints examined include cancer, neurotoxicity, immunotoxicity, genetic toxicity, and reproductive effects.

Mechanistic studies are often incorporated into the testing scheme. For example, it is hypothesized that decreases in the hormone, melatonin, could play a role in development of breast cancer. Animal studies indicate that exposures to electric and magnetic fields reduce nocturnal production of melatonin. The NIEHS/NTP, in conducting 2-year studies of electric and magnetic fields, has incorporated measures of melatonin levels in these studies in order to investigate this avenue of inquiry. Preliminary findings are being evaluated and are expected to be reported in 1995.

The NIEHS/NTP database of approximately 450 long-term studies offers a rich resource for retrospective analysis. Recently NIEHS intramural scientists reviewed this database to examine which classes of chemicals caused mammary tumors in rodents and, by extension, would be probable human breast carcinogens. A total of 30 mammary carcinogens were found Based on this analysis, the following classes of chemicals could play a role in some cases of breast cancer: halogenated hydrocarbons, aromatic amino-/nitro-compounds, and epoxide-forming chemicals

#### **Initiatives**

Requests for Applications

In Fiscal Year 1993, NIEHS and NCI awarded six grants as a result of Requests for Applications (RFA) CA/ES 93-024, titled "Environmental Factors and Breast Cancer in High-Risk Areas." This research program focuses on the association of environmental factors, primarily exposure to organochlorine pesticides and electromagnetic radiation breast cancer risk in the Northeastern United States. Several investigators will be studying biomarkers of susceptibility, oncogenes, and tumor suppressor genes in an effort to understand the gene-environment interactions.

In Fiscal Year 1994, NIEHS awarded six grants in response to RFA ES 94-004, titled "Timing of Exposures to Environmental Agents and Breast Cancer." This RFA called for basic mechanistic research on the role of environmental agents on normal and abnormal breast development, with particular emphasis on the importance of timing of these exposures during critical developmental periods. Agents that are being studied include pesticides and PCBs, polyaromatic hydrocarbons, and electromagnetic and ionizing radiation.

NIEHS also co-sponsored RFA CA/ES/AG 94-05 with NCI and the National Institute on Aging to stimulate the development of research programs within NCI-designated cancer centers on the role of environmental factors in breast cancer development. NIEHS funded four programs with NCI. In Fiscal Year 1994, NIEHS co-sponsored a workshop, "Women's Health: Occupation and Cancer."

### Workshops

 Environmental Risk Factors for Osteoporosis, 1993

Sessions were devoted to bone metabolism and osteoporosis, bone lead mobilization during bone building and osteoporosis, calcium and estrogens in osteoporosis development, cadmium, aluminum, and fluoride as risk factors in osteoporosis, and other general considerations of environmental interactions in osteoporosis development.

 Women's Health: Occupation and Cancer, Co-Sponsored with the National Cancer Institute and the National Institute on Occupational Safety and Health, November 1993

The purpose of the conference was to present epidemiologic research findings on cancer risks of women working in various occupations. The conference also focused on occupational factors and occupation as a surrogate for lifestyle factors in the etiology of many female cancers, such as breast, cervix, and ovary. The proceedings of this conference will be published in a three-volume supplement in the Journal of Occupational and Environmental Medicine in 1995

Priorities in Health Effects Research-Ionizing Radiation, March 1994 Radiation biologists and epidemiologists from universities, federal agencies, and agencies abroad were invited to discuss gaps in radiation research with special emphasis on follow-up of populations exposed to accidental blasts, such as in Chernobyl. One of the recommendations of this expert panel was to expand our current knowledge of the effects of radiation on reproduction. This would include research on ferulity, hormonal perturbations, pregnancy outcomes, and cancers of the female reproductive organs. Since exposure to a high dose of ionizing radiation (as in the atomic bomb survivors)

is a known risk factor for breast cancer, research is needed on risk in cohorts with low-level chronic exposures.

## NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Reduction of morbidity and mortality associated with breast cancer relies on prevention, early diagnosis, and effective treatment of the disease. The use of these approaches requires a basic understanding of the etiology of breast cancer—the predisposing factors, the cellular processes that operate in uncontrolled growth of breast tissue, and the mechanisms that promote tumor cell metastasis. The National Institute of General Medical Sciences (NIGMS) supports a broad array of fundamental research in cellular and molecular biology, biochemistry, pharmacology, molecular biophysics, and genetics that impacts on virtually all areas of breast cancer research. NIGMS also supports interdisciplinary research training at the predoctoral and postdoctoral levels that provides the personnel for biomedical research relevant to studies of breast cancer. Following is an overview of major areas of NIGMS-supported research and research training, with selected discussion and examples that illustrate the importance of these areas of basic research to the prevention, diagnosis, and treatment of breast cancer.

## Accomplishments

## NIGMS-Supported Research in Cell Biology

Almost every aspect of cell structure and function, from the outer plasma membrane to the activation of genes in the nucleus, must be investigated in order to understand the transformation of a normal cell to a cancerous one. Major factors in the etiology of breast cancer involve activation of cells by hormones, in particular estrogen, and by growth factors, such as epidermal growth factor, fibroblast growth factor, and insulin-like growth factor. An understanding of the invasion and metastasis of tumor cells relies on knowledge of cell adhesion and cell motility. The following are examples of aspects of cell structure and function that impact on understanding cancer cell transformation and metastasis in general, and breast cancer in particular.

#### Cell Division

The cell cycle is highly regulated in normal cell growth and division. Uncontrolled cell division in cancer cells is due mainly to defects at the G1/S restriction point of the cell cycle, where DNA synthesis is initiated. Much of what has been learned about cell cycle control stems from basic genetic and biochemical studies in lower organisms, such as yeast, and the identification of highly conserved homologous mammalian genes and gene products. Continued basic cell cycle research in model systems, as well as in mammalian cells, should define the mechanistic role of tumor suppressor genes in controlling cell division, and the identification and characterization of growthpromoting genes in gene activation and amplification. Such studies should result in molecular strategies for gene therapy and inhibition of key biochemical steps in unregulated cell division.

A second critical control point in the cell cycle is the initiation of mitosis. Further knowledge of the processes required for chromosome segregation and cell division may provide targets for inhibition of cell division and prevention of abnormal chromosomal segregation leading to oncogene translocations and cancer. Microtubule proteins and molecular motors also play a role in cell motility related to tumor cell metastasis. These molecules therefore are targets for chemotherapeutic agents such as taxol, vinblastine, and colchicine that interfere with the synthesis and function of cytoskeletal proteins. As new families of cytoskeletal proteins are discovered, new opportunities will arise for targeted drug design aimed at interfering with abnormal cell growth, division, and metastasis.

#### Cell Death

Controlled cell death, like controlled cell division, is a feature of normal cells. Programmed cell death, called apoptosis, occurs in development, in response to hormonal signals, and in the immune system. Cancer cells apparently have aborted cell death programs that contribute to uncontrolled cell division. A recently identified oncogene, bcl-2, inhibits apoptosis, while the p53 tumor suppressor gene may promote apoptosis. Furthermore, certain chemotherapeutic drugs appear to function by activating programmed cell death pathways. Much of what is currently known about apoptosis comes

from studies in the invertebrate, *C* elegans. Continued studies of programmed cell death in a variety of model systems should provide important new insights into mechanisms of controlled tumor cell growth and the development of new treatment strategies.

#### Cell Activation

Normal cell activation ensues from the delivery of a signal to a membrane receptor and the coupling of that signal to a biochemical cascade that results in gene activation, synthesis of new proteins, and cell growth and division. Cancer cells are constitutively activated, or "turned on," by a variety of growth factors and hormones, and by expression of mutated growth control receptor genes, resulting in uncontrolled cell growth and division. Knowledge of receptor structure and function and the specific steps in the signal transduction pathway should provide new insights into the prevention and treatment of breast cancer

#### Cell Differentiation

Tumor cells generally are dedifferentiated, factors that promote cell differentiation also slow tumor cell growth and invasion. Basic studies on differentiation factors, such as transforming growth factor beta (TGF-B) and retinoids of the vitamin A family in normal cell differentiation and development, will provide important information on the role of these molecules in breast cancer. Studies of TGF-B in normal cell differentiation and development are of particular interest since TGF-B induction by tamoxifen and retinoic acid may provide a mechanism for the prevention and treatment of breast cancer by these agents.

#### Cell Adhesion

The adhesion of cells to each other, to basement membranes, and to the extracellular matrix is an important factor in tumor formation. invasion and metastasis. A wide range of basic studies addressing mechanisms of cell adhesion are therefore relevant to breast cancer research. For example, overexpression of laminin receptors is associated with increased tumor invasiveness. In contrast, expression of some adhesion molecules, such as the cadherins. reduces tumor invasiveness. Several classes of glycoprotein adhesion molecules, such as p-selectin, mediate formation of intravascular tumor emboli and establishment of metastatic sites. Further knowledge of the structure and function of adhesion molecules, such as the

integrins, cadherins and selectins, as well as research on the structural and biochemical components of the cell that mediate attachment to the extracellular matrix, should provide the basis for intervention in tumor invasion and metastasis

#### Cell Motility

A second important parameter in tumor cell metastasis is cell motility. Many growth factors, such as platelet-derived growth factor and insulin-like growth factor promote cell motility A recently discovered tumor suppressor gene. nm23, functions by suppressing cell motility, and therefore, tumor cell metastasis. The nm23 gene product is nucleoside diphosphate. kinase, and at least one substrate for this kinase is dynamin, a newly discovered molecular motor protein involved in intracellular transport as well as cellular motility. As the members of the evtoskeletal protein and molecular motor families grow, it is expected that new opportunities will rapidly arise for the design of drugs that target the cell motility apparatus and interfere with tumor cell invasion and metastasis

#### Intracellular Transport

One of the prognostic indicators for breast cancer is the multidrug-resistance gene (mdr). This gene encodes a transporter molecule that pumps chemicals, such as cytotoxic chemotherapeutic agents, out of the cell. The mdr gene also may be important in cancer prevention as it pumps unwanted carcinogens out of normal cells. Knowledge of the mdr gene and its encoded transporter stems, in part, from studies of cellular transport in yeast. Continuing studies on molecular motors, such as the kinesins and dynamin, also may have payoffs in understanding how drugs and carcinogens are transported in and out of cells.

## NIGMS-Supported Research in Biochemistry, Chemistry, and Pharmacology

#### Enzymology

Many enzymes are involved in the conversion and clearance of carcinogens, and in biochemical mechanisms associated with tumor cell growth and metastasis. The study of enzyme kinetics, reaction mechanisms, and substrate specificity will enable a rational approach to the design of therapeutic and preventive agents. For example, reducing enzymes are involved in the detoxification of oxidative metabolism carcinogens while other enzymes stimulate tumor growth.

and proliferation. The metalloproteinase enzymes, for example, collagenase, promote tumor cell invasion and metastasis. DNA repair enzymes play a key role in the cell's response to carcinogens, and faulty repair may lead to gene mutations with oncogenic potential. These are just a few examples of enzyme targets for the design of inhibitors or activators that may be useful in the treatment of breast cancer. In addition, studies are underway to identify gender-related differences in the metabolizing capacity of therapeutic drugs, particularly with respect to the P-450 enzymes.

## Chemistry and Pharmacology

Natural plant and animal products are a major source of bioactive agents with anti-tumor activity. The clinical exploitation of such agents depends on the ability to chemically purify and synthesize them. A prime example of this is taxol, derived from the bark of the yew tree. While very promising in the treatment of ovarian and breast cancer, only limited natural supplies were available. Improved approaches for isolation, purification, and synthesis have enabled widespread clinical trials of taxol. Many other natural products are targets for synthesis and clinical testing, and further studies on these and other agents will be needed. Such knowledge comes from basic chemical and pharmacologic research on a variety of related compounds.

## NIGMS-Supported Research on Molecular Biophysics

#### Structural Biology

In order to fully understand how biologically active molecules work, and how to interfere with or promote their function, the structure must be known at the molecular level. Research into the structure and function of receptors, growth factors, kinases, and transcription factors will greatly facilitate an understanding of the mechanisms operating in the development of breast cancer, and in strategies for treatment and prevention. Basic structural research has led to the determination of the structures of several growth factors, and receptor structure is being investigated at the molecular level. The structure of the glucocorticoid receptor recently was determined and should prove informative for an understanding of the function of the superfamily of steroid hormone receptors, including those for estrogen and progesterone. Structures of other receptor molecules, such as

those for growth factors and tyrosine kinases, will be of great importance for breast cancer research. The study of molecular structure for rational targeted drug design already is underway in the search for agents active in the prevention and treatment of AIDS. A similar approach should be applicable to other clinical problems, including breast cancer.

### **Imaging Techniques**

Research in molecular biophysics requires spectroscopic and crystallographic techniques. An outgrowth of these studies has been advances in magnetic resonance imaging (MRI) techniques. A newly discovered approach, called relaxographic imaging, should provide a more sensitive method for the earlier detection of breast cancer. Research on the development of photoprobes, fluorescent dyes, and other molecular tags also should yield new opportunities for the detection and treatment of cancer.

## NIGMS-Supported Research in Genetics and Molecular Biology

The genetics of breast cancer encompasses the identification and characterization of genes that determine disease susceptibility; the regulation and expression of genes involved in transformation, growth, and metastasis of tumor cells; and genetic strategies for treatment and prevention.

#### **DNA** Repair

DNA breaks and repair occur in the course of normal cell growth and division. However, incorrect DNA repair can result in mutations and translocations resulting in tumor formation. Research on DNA repair genes, the functions of the proteins they encode, and the mechanisms of mutagenesis will lead to the design of new anticancer drugs.

#### Gene Expression

Many oncogenes are normal cell genes that become oncogenic when they are either underor over-expressed. Other oncogenes encode or activate transcription factors that lead to uncontrolled growth, cell division, or motility. Further research on these genes, their protein products, and the mechanisms that regulate their expression will provide novel opportunities for gene therapy and gene replacement.

#### Gene Amplification and Translocation

Certain genes become oncogenic when amplified or translocated to a new chromosomal position subject to altered gene control. Research into mechanisms that promote abnormal gene and chromosome segregation, and gene amplification may lead to the design of cancer prevention agents.

Gene Targeting, Replacement, and Therapy As genes are identified that either promote or inhibit tumor formation and metastasis, they will become targets for gene replacement or modification. Genes with clear prognostic, causative, or preventive roles may be up- or down-regulated, or replaced to prevent and treat breast cancer. Research on DNA recombination mechanisms will provide new techniques for gene therapy approaches.

NIGMS-Supported Research in Physiology NIGMS supports research into mechanisms of wound repair in response to trauma and burn injury. This research encompasses studies of growth factors that are highly relevant to breast cancer research. For example, tumor invasiveness and metastasis are strongly correlated both with the density of blood vessels within a tumor and the angiogenic factors that promote both blood vessel growth and metastasis Another aspect of wound repair involves cellular adhesion mechanisms and structure and function of the extracellular matrix These mechanisms also regulate tumor cell interaction with the basement membrane and the propensity of cancer cells to migrate out of a local tumor site. Further studies on growth factors and adhesion mechanisms may give rise to promising chemotherapeutic interventions.

#### Research Training

NIGMS extensively supports interdisciplinary research training of predoctoral and postdoctoral scientists. These training areas provide the personnel needed to attack the problem of prevention, diagnosis, and treatment of breast cancer. The Medical Scientist Training Program provides training of students with both a medical and scientific background. These future scientists, with both medical and doctoral degrees, will be ideally poised to address research problems in cell biology, biochemistry, immunology, biophysics, molecular biology, and genetics and to relate their results to clinical areas. The predoctoral training program in cell biology, molecular biology, and biochemistry encompasses research training on cellular mechanisms, enzymology, and molecular mechanisms relevant to understanding cell growth, activation, division, and motility. The

genetics training program at the predoctoral level prepares future scientists to understand the genetic mechanisms operant in the inheritance of genetic factors, transcriptional control, mutagenesis. DNA structure, recombination and repair, and the role of genes in cell division and differentiation. Postdoctoral training programs in genetics foster the development of those with medical and doctoral degrees with expertise in genetic approaches to disease. The training program in molecular biophysics focuses on the development of scientists able to determine the three-dimensional structures of biologically active molecules and the relationship of the structure to function. These future structural biologists will be in a position to design drugs rationally to treat diseases such as breast cancer. The NIGMS training program aimed at the chemistry/biology interface has the goal of fostering more chemists with a knowledge and understanding of biological systems. This is an area that also will be critical for the design of new drugs and diagnostic and preventive approaches. This program complements the existing training program in the pharmacological sciences that prepares young scientists to investigate the biochemical systems that are amenable to pharmacological intervention and to investigate the pharmacology of drug action and drug toxicity

## National Institute of Mental Health

The National Institute of Mental Health (NIMH) conducts research on the causes, diagnosis, treatment, and prevention of mental disorders. Mental illnesses are complex disorders involving the capacities to think, feel, and to act By necessity, the research focus of NIMH is broad, encompassing exploration of the fundamental biology of the brain and basic processes of behavior, as well as the interaction between biology and environment. Research supported by NIMH has led to major advances in effective therapies and preventive strategies, as well as important insights into biological and psychological foundations of behavioral disorders that affect developmental processes, health status, and quality of life.

Research questions related to the risks for prevalence and treatment of mental disorders in women historically have been an important part of NIMH's scientific agenda. Over the past decade, development of a sophisticated

epidemiologic database has provided a clearer picture of the extent of the various types of mental illnesses in the U.S. adult population overall (not just those seeking clinical care), and of specific real differences between men and women in the prevalence and expression of these disorders.

Valuable information also has been gained about the roles and interactions of biological and environmental factors in mental illness and health, and about the implications of sexrelated biologic factors in understanding the causes and in developing effective treatments for mental illnesses. These trends, along with a climate of growing recognition of the importance of conducting research and evaluating treatments in women, have primed the mental health field for an era of productive, focused study of women's mental health concerns.

Old barriers to needed research are now coming down. Historically, out of concern for women during their childbearing years, they have been excluded from early stages of drug development, and studies of medication effects on women have been curtailed. Other barriers have included the complexity and cost of studying interactions of medications with the menstrual cycle in large numbers of women, and a paucity of data from female animals, given the variability associated with the estrus cycle.

While overall prevalence of major mental disorders are equivalent for women and men, important gender differences are seen in the prevalence of specific disorders. Conditions such as major depression and dysthymia affect approximately twice as many women as men. An estimated 6 percent of U.S. women, in contrast to 3 percent of men, will experience a major depression during their lifetime. At least another 6 percent of women have dysthymia, a less severe but often more chronic form of depression. Schizophrenia, too, appears to be marked by gender differences, but in manifestations and course, not prevalence.

Anxiety, panic, and phobic disorders also predominate in women, affecting two to three times as many women as men. The eating disorders anorexia nervosa and bulimia nervosa (conditions that may be related to obsessive-compulsive behavior) affect women almost exclusively. Anorexia and bulimia together affect 0.5 to 2 percent of adolescent girls and young women, and the prevalence of both is increasing. These disorders can become life-

threatening, indeed, even lethal; recovery is slow and relapse is common.

Mental disorders in women are inextricably linked to their own physical health and to the health and well-being of their families. In fact, because women are often care givers for their parents and children concurrently, a woman's mental disorder may affect two or three generations. Conversely, the burdens of care giving often can amplify mental disorders.

## Accomplishments

### Depression and Related Disorders

Out of the recent wealth of clinical and epidemiological data related to mental health, gender emerges strongly and consistently as a major risk factor for depression, with depressive disorders affecting more than twice as many women as men. Yet despite the robustness of this finding, much less is known about specific etiologic factors that underlie this association. Clearly, gender is but a proxy term for a system of psychosocial and biological variables. Further complexity stems from the reality that the mood disorders represent a broad spectrum ranging from those that arise primarily in reaction to environmental stressors to those related more strongly to endogenous factors. The role and relative weight of various gender-specific factors may differ across this spectrum and may also influence symptom patterns, comorbidity, course, treatment response, and outcome.

In both community and clinical samples, gender-specific risk for mood disorders varies with the specific type of disorder. Men and women differ little in rates of bipolar disorder, but vary strikingly in the broader spectrum of unipolar disorders. Nonetheless, there is evidence that men and women with bipolar disorder may differ in clinically significant ways in phenomenology, comorbidity, and course. The course of bipolar illness in women is characterized by more depressive and fewer manic episodes, and women are more likely to develop the rapid-cycling form of the illness. Gender differences in prevalence are more pronounced in unipolar depressive illness, with some early evidence that differences may be greater in the less severe forms, as well as atypical and seasonal affective disorders.

Clinical studies have found that women predominate in seasonal and rapid-cycling bipolar disorder and in dysphoric mania. These forms of mood disorder are characterized by a pronounced disruption of circadian rhythms and sleep patterns. While it is clear that gonadal steroids regulate circadian rhythms in some animals, it is currently unknown if they do so in humans, as well. Extrapolating from a limited database. NIMH scientists have proposed the hypothesis that estrogen shortens the circadian period, lengthens the sleep phase, advances sleep onset, and consolidates sleep. This hypothesis suggests that there should be gender differences in circadian rhythms, an idea yet to be examined, but one certainly worth pursuing. Estrogen is known to influence the function of serotonergic circuits in the brain Perhaps. therefore, it is not coincidental that the suprachiasmatic nucleus, the brain's central circadian pacemaker, contains estrogen receptors and is innervated by serotonergic neurons. Further testing of this hypothesis promises to be fertile ground for research on both mood disorders and circadian rhythms

Because the gender difference in depression is not expressed until after puberty, it is hypothesized that hormonal factors are involved in women's greater vulnerability. Psychosocial factors, too, likely are involved since the femaleto-male ratio for depression has narrowed over the last generation. Among psychosocial factors that have been cited are that women are more likely than men to have multiple roles in the home and at work, to be poor, to be at risk for violence and abuse, and to be burdened with single parenthood. These stressors interact with an individual's vulnerability in the genesis of depression.

Major depressive illness tends to be a fundamentally recurrent condition. The persistence of major depression in the general population is high; conservatively estimated, 20 percent of depressed people will remain depressed 1 year after an episode of illness. For women, poor recovery is associated with additional specific sociodemographic factors—having less than a high school education and an unstable marital history—that do not appear to influence recovery among men. Depression becomes chronic for almost 30 percent of depressed women with these risk factors. In addition, for women more than men, major depression and other mental illnesses, such as anxiety disorders and eating disorders, are more commonly linked to substance abuse.

Depression in women is a debilitating condition and affects not only their own functioning,

but their loved ones Maternal depression, for example, was found to have an impact on infants. NIMH-supported investigators suggest that infants born to depressed mothers may show depressed behavior (flat affect and lower activity levels) as early as birth possibly due to genetic and/or prenatal environmental factors In a study designed to compare infants born to depressed and nondepressed mothers on the Brazelton Neonatal Behavior Assessment Scale. infants of depressed mothers demonstrated poorer performance on orientation, motor tone. and activity clusters. In addition, the infants of depressed mothers also showed more irritability, less robustness, and less endurance (unavailability, lethargy, and stress behavior) during the examination. The investigators suggest that the depressive symptomatology shown by these infants at birth might contribute to mother-infant interaction disturbances, which might aggravate the mother's depression

Because women live considerably longer than men, they are more likely to experience widowhood, a stressful life event associated with impaired psychological, physical, and social functioning, and increased risk for mortality. Depression is a common response Many elderly women, especially those who are widowed, need outpatient care for major depression but frequently lack access to it. A recent study has shown that partial hospitalization (day treatment)—a program of intensive. coordinated, and structured mental health services in an outpatient setting—can be effective in treating such patients. A program providing group therapy 2 days a week through three phases of treatment—i e, intensive (3 months), modified (3 months), and open-ended maintenance—achieved clinical improvement in 57 percent of patients during the initial 3 months.

A long-term controlled clinical trial has found interpersonal psychotherapy (IPT) to be an effective treatment for women with recurrent unipolar depression. During treatment of an acute depressive episode, only 20 to 25 percent of the women, or half as many as predicted, required the addition of anti-depressant medication to IPT to achieve remission. During a 2-year follow-up, maintenance IPT (used at three different frequencies, or "doses") is proving effective in preventing relapse, including two patients who delivered healthy babies without recurrence of depression during maintenance treatment. A variety of

biological and psychosocial variables are being analyzed to identify those women most likely to benefit from this treatment, as well as to define a dose/response curve for IPT.

In the first prospective, controlled antidepressant medication trial for the prevention of postpartum major depression, another group of investigators is comparing 20 weeks treatment with nortriptyline versus placebo in new mothers with a previous history of postpartum depression. The first five randomized women will be delivering soon (incoming subjects are also being tracked by the television newsmagazine, "Prime Time Live," so that this NIMH-supported research will indirectly further public awareness and understanding of postpartum disorders). In open-label trials, these investigators recently have reported that antidepressant medication, begun within 24 hours of delivery by women with a previous history of postpartum depression, reduced the incidence of depressive recurrence by tenfold during a 3-month follow-up.

## Premenstrual Syndrome (PMS)

For a subset of women, especially those with a prior lifetime history of depression, the premenstrual phase of the menstrual cycle may be a period of increased vulnerability for the appearance of a period of depressive symptoms or for the worsening of an ongoing period of depression. In fact, several studies have found that anywhere from 14 to 45 percent of women complaining of premenstrual syndrome met the diagnostic criteria for late luteal phase dysphoric disorder. The wide range highlights the need for better definition and uniform assessment methods for mood changes associated with premenstrual syndrome.

Though there are little data relating serotonin activity to premenstrual symptoms, there is a large database showing that postsynaptic response to serotonin does vary with the menstrual cycle, particularly in the late-luteal phase. In addition, recent neurobiological studies have shown that levels of serotonin receptor subtypes respond differently to gonadal steroids. Recent NIMH-funded studies found. for example, that the cortical density of serotonin type-1 receptors rises with increasing levels of estrogen while the density of serotonin type-2 falls. The changes in type-1 receptor density occur 1 to 2 days following administration of estrogen and are consistent with the assumed changes in activity of the serotonergic system

during the late-luteal phase. Thus, a promising approach studying premenstrual syndrome might be to simulate it with receptor-specific serotonin agonists and antagonists. Results of a small single-blind trial of fluoxetine, a serotonin reuptake inhibitor, showed the promise of this approach. Nine out of 10 women with late-luteal phase dysphoria who were treated with fluoxetine experienced significantly decreased symptoms. All the women participating in the study elected to continue drug therapy after the study was completed.

Using a nonpharmacologic approach originally demonstrated as effective in seasonal depression, a series of studies have identified bright-light treatment as helpful for some women with PMS-associated depression. Light treatment exerted no effect on control groups of women without this diagnosis. However, as a dim-light condition, intended as a placebo control, was also associated with a significant reduction in depression ratings, further studies are required to definitively conclude that light treatment exerts a specific therapeutic effect in PMS.

## Eating Disorders

The eating disorders anorexia nervosa and bulimia can be characterized as women's disorders because they are rarely seen in men. People with anorexia starve themselves into extreme weight loss, a behavior that is associated with an irrational fear of becoming obese and a severe body-image disturbance of near psychotic proportions. Those with bulimia engage in repeated binge-eating episodes followed by self-induced vomiting, fasting, or using laxatives or diuretics. It is not uncommon for the two disorders to occur together.

Anorexia nervosa, with one of the highest mortality rates of any psychiatric disorder, overwhelmingly (>90 percent) affects women, and its incidence appears to have increased over the last generation. Moreover, despite its recognition for hundreds of years, there remains no generally effective, specific treatment for this serious disorder. Inpatient management and refeeding are usually necessary acute interventions in these individuals. The challenge then becomes to maintain body weight and normal eating behaviors. An ongoing study supported by NIMH is comparing the selective serotonin reuptake inhibitor antidepressant, fluoxetine, with placebo in the 1-year maintenance treatment of women with anorexia

nervosa who have recently regained normal weight. Preliminary results show a trend toward effectiveness of fluoxetine, with a slight majority (7 of 12) of fluoxetine completers of the 52-week trial maintaining their improvement.

Bulimia nervosa, the "binge-purge" syndrome, is prevalent in 1 to 3 percent of late adolescent and young adult women; again, fewer than 10 percent of patients are male. In contrast to anorexia, a variety of treatments, specifically antidepressant medications and cognitivebehavioral therapy (CBT), have proven beneficial in the short-term treatment of bulimia. Current efforts are targeted to defining optimal length of treatment and the relative efficacy of biological and psychosocial interventions. In one of the largest and longest studies to date. 61 patients (all women) with bulimia were randomly assigned to treatment with desipramine (either 16 or 24 weeks duration), CBT. or the combination, and followed for 1 year Acutely, combination treatment was superior (70 percent response rate) to either CBT (55 percent response) or desipramine (40 percent response) alone. At 1-year follow-up, the best results again were seen in the combined treatment group (CBT + 24 weeks of desipramine), where 78 percent of patients were free of binge eating and purging. The poorest outcome (18 percent response) was seen in the shorter-term (16 weeks) desipramine-only group, with the other groups between these two extremes. Thus, the value of both psychopharmacological treatment and psychotherapy for bulinua was confirmed along with the necessity of a 6-month trial of medication.

Recently, a new category of eating disorder has been described in the literature. Binge-eating disorder is a variant of bulimia lacking the purging phase, such that most individuals with this syndrome are obese. Preliminary findings from NIMH-supported investigators have identified two types of group psychotherapy—cognitive-behavioral and interpersonal—as effective in binge-eating disorder. A currently funded comparison trial of these two treatments is under way, aimed at identifying temporal patterns of change and predictors of response.

It is well established that individuals with bulimia recover more often than do those with anorexia or both disorders. However, a recent NIMH-funded survey of women with anorexia found that nearly half the anorexic and mixed subjects no longer met full diagnostic criteria for at least 8 consecutive weeks during the first year after completing psychotherapy for the disorder. Total recovery at 1 year—no symptoms of the disorder—was seen in 56 percent of women with bulimia and 10 percent of women with anorexia alone. It is not known how many of these "recovered" patients stay symptom-free beyond 1 year, suggesting that a long-term monitoring effort is needed to gain a better understanding of the prognosis for these disorders

### Anxiety Disorders

The fact that phobias, a type of anxiety disorder, affect two to three times as many women as men, and that they are extremely common mental illnesses, makes research on these disorders a particularly important issue for women's mental health

NIMH-funded investigators have made use of a large registry of twins to search for possible genetic factors involved in phobias and other anxiety disorders. Interviews with more than a thousand pairs of female twins showed that there was substantial comorbidity between major depression and four types of phobia agoraphobia, social phobia, animal phobia, and situational phobia. Using a powerful statistical method, known as bivariate twin analysis, to tease apart environmental and genetic factors that major depression and phobias might share, the investigators determined that only about 25 percent of the observed comorbidity between major depressive disorder and phobias results from genetic factors, with shared environmental risk factors responsible for the majority of the comorbidity. In contrast, bivariate twin analysis on the same group of women showed that genetic risk factors accounted for all the comorbidity of major depression and generalized anxiety disorder. This finding suggests that in women the risks for developing major depression and generalized anxiety disorder are influenced by the same genetic factors. Environmental influences then determine whether a vulnerable woman develops major depression or generalized anxiety disorder. These results support the hypothesis that though generalized anxiety disorder and phobia share many common symptoms, they may be different disorders.

Posttraumatic stress disorder (PTSD) is an anxiety disorder first characterized in male combat veterans, but also has been found to

affect women victims of severe trauma. Core symptoms of PTSD include experiencing a distressing event that involved actual or threatened death or serious injury or a threat to one's physical integrity that involved intense fear, helplessness, or horror; reexperiencing the trauma in nightmares, intrusive thoughts or flashbacks; and numbing of responsiveness or avoidance of thoughts or acts related to the trauma. PTSD can be one of the most debilitating and harmful effects of sexual assault. An NIMH-funded study of rape victims showed that 94 percent of these women met the criteria for PTSD 13 days after their assault. Three months later, half of the women who had been raped were no longer suffering from symptoms of PTSD, though half still were. Moreover, those rape victims still suffering from PTSD months after their assault were unlikely to recover without counseling.

Although many forms of intervention exist for rape-related PTSD symptoms, only a few well-controlled studies have been conducted to systematically evaluate the treatment response of women who have been the victims of sexual assault. Overall, cognitive-behavioral interventions for rape-related PTSD, with single or multiple treatment components, have been found to produce a decrease or remission of posttrauma problems when compared to no treatment. Cognitive desensitization, in which the victim practices relaxation techniques in a safe environment while mentally reliving the trauma, weakens the fear response triggered by these terrible memories. Few women receive such therapy, however, since the most common professional intervention for rape victims is the limited crisis-intervention counseling offered in rape crisis centers. Recent data show, however, that such limited therapy is not enough to help many women overcome PTSD following sexual assault, suggesting that the nation's rape counseling network needs to be enhanced.

#### Physical and Sexual Assault

It is now well established that childhood sexual abuse can have effects that last far into adulthood. An NIMH-sponsored comparison of women with histories of child sexual abuse and a control group without such histories showed an association between childhood sexual abuse and the adult women's symptoms of anxiety and depression. The study found that adulthood symptoms of depression and anxiety

had little to do with whether the abuser was a relative or not, but depended more on the psychosocial dynamics of the family. Women who described their families as less cohesive, more conflicted, and having more rules and procedures that governed family life exhibited the highest levels of depression and anxiety. These findings fit a model in which family environment can buffer the relationship between sexual abuse and later symptoms and suggests that interventions designed to help young victims of child abuse need to involve the entire family if the goal is to avoid future psychological problems.

Studies such as this take on greater meaning when one considers that women who are sexually victimized as children are at greater risk than other women for further victimization as young adults. A survey of women college students found that nearly 13 percent were sexual assault victims during their first year in college. The single best predictor of this was adolescent sexual assault, and the best predictor of adolescent victimization was childhood victimization. The data clearly indicate that waiting until college to begin "date-rape-prevention" programs is too late for significant numbers of women.

A companion study of freshman men, meanwhile, found that university males who are sexually, physically, or dually assaultive toward their female companions are also apt to be assaultive in general, to use weapons, damage property, commit theft, and engage in rowdy and publicly drunken behavior. Furthermore, precollege involvement in both sexually and physically assaultive violence was the single best predictor of later dating violence. These findings argue against the interpretation of date and acquaintance rape as the consequence of miscommunication between dating partners. These findings seem, instead, to lend support to the state-dependency explanation for violent encounters between men and women that links past and future criminality. They also imply strongly that rape prevention programs must target assaultive males, and they must do so early in a young man's life.

Once a woman is criminally assaulted, her need for medical care goes beyond the traditional focus on emergency medical attention and forensic evaluation. One recent NIMH-funded study found that severely victimized women members of a health

maintenance organization made twice as many physician visits a year as men and had outpatient medical expenses that were two-and-one-half times greater. These women had a number of persistent conditions diagnosed disproportionately among rape victims, including chronic pelvic pain, gastrointestinal disorders, headaches, chronic pain, psychogenic seizures, and premenstrual symptoms.

Medical management of all types of victimized women can be improved by attention to the underlying etiology of their symptoms, which requires that physicians identify a history of victimization and provide access to appropriate support services. Because all forms of violence against women are prevalent among primary care populations and victimization is clearly linked to health, health care providers cannot afford to miss this relevant history

## AIDS-Related Research on Women's Health

Recent evidence from the Centers for Disease Control and Prevention (CDC) indicates that AIDS is one of the leading causes of death among women 25 to 44 years of age in the United States. The leading cause of HIV infection in women is heterosexual transmission. Other statistics from CDC indicate that the national pattern of HIV infection and AIDS is changing. The percentage of AIDS cases attributed to heterosexual contact has increased 21 percent from 1990 to 1991. Anonymous testing of blood samples from 35 U.S. colleges campuses revealed that 1 in 500 college students were found to be infected with HIV. The number of women diagnosed with AIDS jumped 50 percent between 1989 and 1991, with heterosexual transmission a major contributing factor. The overall seroprevalence estimate for childbearing women nationwide is 0.15 percent, which reflects nearly 6,000 births per year to infected women in 1989 and 1990.

Because of the paucity of data on sexual behavior of women, and because the practical and affordable women-controlled methods for barrier protection are limited, it has been difficult for health providers to develop effective AIDS preventive interventions for women. NIMH has initiated an aggressive program to address the problems of HIV infection in women and to initiate interventions to attenuate the spread of AIDS to this population. The most effective

way to prevent AIDS today is through behavior change. NIMH-supported research studies of behavioral epidemiology have identified highrisk HIV-related behaviors, cultural norms, values, and communication patterns in subgroups of people from different geographic areas. Critical findings from these surveys indicate that different people respond to different approaches, and the intensity of the intervention must be titrated to produce the desired change. Results from these studies have enhanced the effectiveness of NIMH-supported individual and community prevention efforts.

NIMH has taken an active role in funding AIDS-related research because issues related to mental health arise at every point in the development of AIDS—from the risk-taking behavior that contributes to HIV transmission. to the early signs of HIV entry into the central nervous system, to the psychological, social, and behavioral challenges faced by all HIVinfected individuals, and finally to the profound late-stage dementia and neurological pathology that affects many Since AIDS was first identified. NIMH has taken the lead in generating a research knowledge base for prevention programs aimed at all high-risk populations, and for improving the delivery of mental health services to those infected with HIV

The goal of NIMH-sponsored AIDS-related behavioral research is to increase understanding of behaviors associated with HIV transmission, with the ultimate goal of preventing further HIV transmission. Knowledge about risk behaviors provides the scientific foundation for the development of effective behavior change interventions. Continued development and refinement of methods for measuring the efficacy of behavior change interventions are a crucial part of this effort.

In a large-scale field trial conducted in 16 small cities in different regions of the country, NIMH investigators found that it is possible to change risk behavior levels in community populations by teaching "opinion leaders" to communicate effective AIDS prevention messages to friends and acquaintances. This means that it is possible to produce change in entire communities by enlisting the efforts of popular and trusted persons to redefine social norms and discourage risk behavior.

An NIMH-supported behavioral epidemiological study of AIDS-related risk behaviors, knowledge, beliefs, and HIV serostatus has revealed that women of all ages and ethnicities are potentially at risk for HIV as a result of unprotected sexual behavior. A prevention program focused on skills designed for innercity women shows that even a brief five-session intervention can be effective in reducing high risk HIV-related behavior. Another intervention received by a group of African-American adolescents at risk for HIV led to significant differences in HIV risk acts over 3 months.

An NIMH Consortium on Prevention consisting of senior preventions investigators has been established to conduct pilot studies to examine specific issues in conducting large scale prevention studies. Women are a major focus of this effort.

An NIMH Multisite Prevention Trial is in a Phase II/Phase III study to test the efficacy of an HIV-prevention program in seven sites with multicultural populations that include African-American and Hispanic women. Women from both STD clinics and primary care facilities are being recruited into this study. While the concepts and skill lessons are the same across populations, the intervention is tailored to meet the needs of specific populations. If efficacy is demonstrated, this will provide major confirmation of the generalizability of this intervention and tailoring technique that is required prior to movement to a community-based adoption of this prevention.

A collaborative effort with the AIDS Research Center in New York has been initiated to develop HIV-prevention strategies for women, and to develop programs to enhance the use of these female-controlled methods. At the AIDS Research Center in San Francisco a study has been initiated to determine cultural factors that may contribute to high-risk behavior and to develop culturally appropriate prevention methods to change HIV risk behaviors in minority women.

A study of inner-city African-American female adolescents is evaluating the efficacy of interventions based on cognitive behavioral model of behavior change with self-report of lower risk behavior. Investigators are conducting a behavioral study of Haitian women in Miami to understand their perception of sexually transmitted diseases and HIV infection to begin to target effective interventions to this group.

## Research Center on Women's Mental Health

The first major mental health services research program that focused on women's services was funded at the University of Pittsburgh in Fiscal Year 1994. The program will (1) bring together clinical researchers, health services researchers, and community leaders involved in provision of services to women; (2) provide infrastructure support for thematic research on treatment effectiveness in women; and (3) establish a unified database for women's services studies. This planned research links treatment effectiveness studies with other funded efficacy studies in women with mood, anxiety, and eating disorders. A central feature of this research program is the plan to conduct studies at three different sites: outpatient psychiatric clinics, primary care health centers, and low income minority housing projects. There are large groups of understudied women at each site, and representation from each is needed to answer pressing questions about how best to help women with mental illness.

#### **Initiatives**

## **Program Announcements**

 Anorexia Nervosa and Bulimia Nervosa Basic Brain, Behavioral, and Clinical Studies

The incidence of anorexia has doubled over the last 2 decades. Studies are encouraged in three major areas: (1) basic brain and behavioral sciences research on neurobiological, endocrinological, and behavioral factors associated with ingestive behaviors and eating disorders; (2) epidemiology and clinical phenomenology; and (3) treatment studies across various stages of the life cycle. PA91–79

 Special Issues in Women's Mental Health Over the Life Cycle

This program announcement seeks to expand the full spectrum of research on issues pertinent to women's mental health and seeks to expand scientific capacity to conduct research on women's mental health concerns by increasing the number of well-trained investigators through institutional research training grants, research career awards, and pre- and postdoctoral individual fellowships. PA91–100

#### **Publications**

## Women's Mental Health Research Rulletin

This publication was launched in fall of 1994 as a semiannual newsletter with two main objectives: (1) to enhance the recruitment, retention, and advancement of women in research and academic careers and (2) to improve the quality of scientifically sound research applications by all investigators researching women's mental health by informing them and other interested persons about NIMH activities in women's mental health research.

## Depression: What Every Woman Should Know

This is the first brochure on women and clinical depression produced by the NIMH Depression Awareness, Recognition, and Treatment (D/ART) Campaign. The brochure was developed to help increase women's awareness of what is known about clinical depression to encourage them to seek early and appropriate treatment

## Conferences/Workshops

## Comorbidity of Eating Disorders (October 19–20, 1992)

The prevalence of anorexia nervosa in females is approximately 0.5 to 1 percent, and that of bulimia nervosa, approximately 1 to 3 percent. Evidence indicates that the incidence of both disorders is rising. Ninety-five percent of patients are female. This workshop focused on the comorbidity between eating disorders and disorders, and personality and chemical dependency disorders. The role of genetics in comorbidity was also considered

• Toward a New Psychobiology of Depression in Women: Treatment and Gender (November 4–5, 1993)

Jointly sponsored by the Division of Clinical and Treatment Research and the Office of Special Populations, this conference reflected an integrative psychobiological approach to the topic. Papers dealt with (1) differences between men and women in clinical presentations, prevalence, and vulnerability factors; (2) sex differences in chronobiology and in the hypothalamic-pituitary adrenal

(HPA) and thyroid axes (HPT) in conferring increased vulnerability for mood disorders in women, (3) the specific role of female gonadal steroids, including cyclic patterns in relation to vulnerability to reproductive-related mood disorders; (4) mood disorders secondary to gynecological or other medical illness; and (5) cognitive or emotional traits on which the sexes may differ and that confer a greater risk for mood disorders on women.

## Gender Differences in Child and Adolescent Depression (March 24–26, 1994)

The goal of this workshop was to define avenues for studying the contributions of maturational as well as other changes to decreased vulnerability of males and increased vulnerability of females for affective disorders. A developmental phenomenon that is not well understood is the gender-related shift in prevalence rates of early onset affective disorders. One of the most frequently proposed hypotheses is that the reversal in the male-female ration, from higher rates for boys in childhood to higher rates for girls in adolescence, is associated with the hormonal changes that are responsible for pubertal development. The increased rates in affective disorders among girls beginning in mid-adolescence similarly are attributed to maturational changes. To explore these and other hypotheses, the Child and Adolescent Disorders Research Branch of the NIMH Division of Clinical and Treatment Research convened the workshop to examine what is known about male and female physical and physiological pubertal changes from childhood to adolescence, as well as about other developmental and social-environmental/ contextual factors (cognitive, family, and peer relations) that may be mediating and moderating influences, and their relation to depressed mood and clinical depression.

## Workshop on Definitions in Panic Disorder Research: Recovery, Relapse, Remission, Recurrence (March 29–30, 1994)

This meeting, jointly sponsored by the MacArthur Foundation and NIMH, was designed to reach resolution on the definitions of recovery, relapse, remission,

recurrence, and responder (to treatment). The meeting could not reach consensus on "recovery" because the experts clearly believed that panic disorder was life-long. Without specifying the temporal boundaries of relapse, remission, and recurrence, the participants agreed to use survival curves as a means of collecting data on the course of illness.

## Standardized Assessment of Dysthymia (May 9–10, 1994)

This conference considered key questions relating to the assessment of acceptable symptom criteria, course definition, and comorbidity of dysthymia. Additionally, acceptable diagnostic and assessment screening instruments for symptomatic assessment and functional impairment in dysthymia, and acceptable definitions of response to treatment of dysthymia were discussed. Consensus on most of the questions was reached.

## Mental Health of Minority Women: Setting a Research Agenda (June 7, 1994)

Sponsored by the Office for Special Populations, this workshop brought together clinicians, researchers, and administrators to advise NIMH on how best to direct research efforts to build a solid base in this underresearched area. The discussions focused on organizational, societal, methodological, cultural, and gender issues important to developing an NIMH research portfolio focusing on the mental health of minority women.

## Mental Disorders During Pregnancy and Postpartum (June 22, 1994) Of great interest in this workshop were the tools used to diagnose mental disorders during pregnancy and the postpartum. Some participants described the spectrum of postpartum depression as ranging from dysphoria, which interfered with daily functioning but did not meet DSM-III-R diagnostic criteria for affective disorders, to florid (affective) psychosis. A diagnostic instrument that can be applied consistently in research and clinical settings and that allows for diagnosis of the spectrum of these disorders by differentiating symptoms (such as fatigue secondary to loss of sleep) is needed.

## Role of Families in Preventing and Adapting to HIV/AIDS (July 20–22, 1994)

This conference, held annually, brings together researchers, community service providers, and family advocates to discuss new research findings on issues of importance to families and formal and informal caretakers. Developing directions for new research and fostering communication and collaboration within the community of researchers are central goals.

- Workshop on Conceptual and Methodological Issues in the Treatment of Women Who Have Experienced Physical and Sexual Assault (September 19–20, 1994)

  This workshop was designed to explore research approaches to understanding the
  - research approaches to understanding the efficacy of treatment for women exposed to physical and sexual violence and to cognitive and emotional processes that influence women's interpretation of their exposure to physical and sexual violence. The goal of this meeting was to encourage new lines of research that will lead to improved treatments for women to ameliorate negative effects of physical and sexual assault.

## Sex Hormones, Aging, and Mental Disorders Workshop (September 26–27, 1994)

This workshop was held to begin development of a research agenda that examines how the biological aspects of gender affect the onset, course, and treatment of mental disorders; both disorders with a late-in-life onset and those with early onset that continues into the later years were targeted. For example, a focus of the workshop was the need to understand the role that naturally circulating and replacement hormones, such as estrogen and progesterone, play in the expression and course of depression, affective disorder, and schizophrenia. The role that hormones play in influencing the course of treatment for these disorders emerged as an area that is likely to yield significant results but which has been significantly understudied—in particular the effect estrogen plays on the pharmacodynamics and pharmacokinetics of psychoactive medications. Furthermore, the workshop

emphasized that although there are gender differences in psychiatric disorders, it is equally important to understand the continuum of biological heterogeneity among women (e.g., reproductive history and differences in levels and ratios of hormones).

## NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

The National Institute of Neurological Disorders and Stroke (NINDS) conducts and supports research on the causes, diagnosis, treatment, and prevention of neurological and neuromuscular disorders. Most neurological diseases and disorders affect men and women equally. However, there are several nervous system disorders that are more prevalent in or of special interest to women Research areas relevant to women's health include multiple sclerosis, pain (especially headache), stroke, and myasthenia gravis. Also of interest are the effect of pregnancy on epilepsy seizure activity and the increased risk for fetal death and abnormalities in mothers taking antiepileptic drugs.

## Accomplishments

## Multiple Sclerosis

Multiple sclerosis (MS) is a disease caused by inflammation and scarring of the thick sheath, called myelin, that encases the nerve fibers, resulting in a slowing of electrical impulses. It is one of the most common neurological disorders of young adults, and is two to three times as common in women as in men. There are about 250,000 to 300,000 MS patients in the United States, with an estimated 200 new cases diagnosed each week. The cost of medical care, including patient rehabilitation and loss of productivity, represent an economic burden estimated to be in excess of \$2.5 billion annually. Research findings imply that the immune system plays a strong role in the pathogenesis of MS.

Recent advances in MS include recognition and definition of the major role played by the immune system in the development of MS lesions, identification of genetic factors related to the immune system that predispose an individual to MS, use of magnetic resonance imaging (MRI) to visualize and follow the development of MS lesions in the brain and spinal cord, the recognition of silent or

asymptomatic disease by sequential studies with MRI, and development of therapies that help reduce some MS symptoms. Studies of immune characteristics of MS patients and abnormalities found in animal models will continue. Other promising areas that NINDS will continue investigating include mechanisms of pathogenesis and plaque formation, role of heat shock proteins, remyelination, genetic susceptibility, clinical studies of cytokines, use of peptides in regulation/blocking of immune responses, development of new monoclonal antibodies, and studies of adhesion molecule function in cell traffic across the blood brain barrier.

The intramural program will continue studies using MRI to examine the natural history of multiple sclerosis during the mild, early, relapsing-remitting phases of the disease. These studies have found that many patients have substantial evidence of disease even during its early, apparently inactive phase. The effect of interferon beta 1b, a recently approved therapy in MS, has now been studied in a group of 14 patients with mild, early, relapsing-remitting MS to test its ability to reduce alterations in the blood-brain barrier as measured by gadoliniumenhanced MRI. In those studied, all have a dramatic reduction in lesions, with complete cessation of disease activity, as measured by MRI, for many These findings suggest an important site of action for beta-interferon, and point to new avenues of research to be pursued NINDS supports an MS multicenter clinical trial that tests an alternate form of beta interferon for treatment efficacy

The process of myelin production by nerve cells called oligodendrocytes involves producing vast amounts of proteins and lipids in the correct proportions needed for a myelin sheath. When one of these proteins is missing, defective, or present in the wrong amount, the sheath cannot be properly formed nor maintained. Intramural scientists have now discovered one way that an oligodendrocyte matches the production of myelin lipids with that of myelin proteins. To accomplish this task, oligodendrocytes employ a complex interaction between certain receptor genes and binding proteins.

#### Stroke

Stroke is a major health problem for both men and women. Every day, more than 1,200 Americans suffer a stroke. About one-third die and another third face permanent disability

Although women in general have a lower risk of stroke than men, because of their longer life expectancy they are vulnerable to the acute effects of stroke and the long-term problems of permanent disability. One type of stroke, subarachnoid hemorrhage, is more common in women. In 1993, NINDS initiated a clinical trial to examine estrogen therapy and stroke.

Subarachnoid hemorrhage, a type of stroke that develops when an aneurysm bursts and bleeds into the space around the brain, occurs twice as frequently in women than in men. In a study of more than 300 women, women with lower estrogen, due either to postmenopausal status or other factors (e.g., smoking), are at higher risk for subarachnoid hemorrhage. Postmenopausal women taking estrogen replacement therapy were at decreased risk. For female smokers, or those who previously smoked, hormone replacement therapy reduced the risk. One theory about the mechanism is that estrogens improve the overall cholesterol profile. This in turn reduces the risk for atherosclerosis (hardening of the arteries), a risk factor for aneurysm formation and rupture. There also may be some overall health-promoting effect of estrogen on blood vessels.

NINDS supports a large stroke research center, one subproject of which is examining the use of oral contraceptives and migraine headaches as risk factors for stroke on a population of young women.

In Fiscal Year 1993, NINDS initiated a randomized, placebo-controlled, double-blind trial ("WEST"—Women's Estrogen for Stroke Trial) with postmenopausal women who have had a recent transient ischemic attack or non-disabling stroke. The goal of this carefully controlled trial is to verify the findings of previous epidemiological studies. The study will follow subjects for up to 5 years to determine if estrogen therapy reduces the risk of death or recurrence of stroke.

## Myasthenia Gravis: Etiology and Pathogenesis

Research is being conducted on myasthenia gravis (MG), a disorder of the neuromuscular junction characterized by weakness and fatigability of skeletal muscles. MG is an autoimmune disorder involving an antibody-mediated attack against receptors for the neurotransmitter acetylcholine. It is not known exactly what factors trigger the autoimmune response. Myas-

thenia gravis, like many other autoimmune disorders, occurs about three times more often in women than in men. There are about 50 to 125 cases per million population, or approximately 25,000 affected persons in the United States.

An animal model of MG has proven to be useful for studying and evaluating the disease. NINDS-supported scientists are applying a number of other approaches to understand MG, including use of electron microscopy of nerve and muscle tissue, investigation of the structure and function of the acetylcholine receptor molecule, elucidation of the role and status of B and T-cell lymphocytes in MG, and other autoimmune phenomena.

## Epilepsy: Role of Hormones and Pregnancy

Recognizing that pregnancy and hormones may affect the course of epilepsy, NINDS has an ongoing program announcement on "Hormones and Epilepsy." Investigators are looking into the changes in seizure patterns due to shifts in hormone production in the menstrual cycle or use of oral contraceptives. Women with epilepsy who take antiepileptic drugs are known to have a small but significant increase in their risk of bearing children with birth defects. Research is in progress to determine the mechanisms of this increased risk and to reduce the risk.

The NINDS Antiepileptic Drug Development Program supports an active screening and clinical trials program for safe and efficacious new drugs. Both female and male animal models are used for toxicology screening. Women with epilepsy are well represented in the clinical trials and appropriate analyses are done to detect sex differences in effectiveness or adverse events.

## Migraine Headache

Results from a survey reported in a 1992 *Journal* of the American Medical Association article suggest that about 17 percent of females and 6 percent of males suffer from one or more migraine headaches per year (lifetime prevalence: 25 percent in women, 8 percent in men). This equates to 8.7 million females and 2.6 million males in the United States that experience migraine headache with moderate to severe disability. Migraine causes intense suffering and difficulty in daily living. Like many forms of pain, it has been difficult to study and treat.

The longstanding theory that migraine is caused by constriction or dilation of blood vessels of the scalp and brain is now being questioned. New evidence points to a possible neurological basis for the disorder. The fundamental pathology may stem from a chemical change deep within the brain, where the body uses the neurotransmitter serotonin abnormally. This may trigger a slow, spreading electrical wave in the cortex, triggering nerve involvement and subsequent neurogenic inflammation that results in pain.

Currently, NINDS supports migraine research projects that are investigating the neural basis for migraine and are exploring drug and non-drug treatment for adult and pediatric migraines. A subproject of a large stroke research center is examining the use of oral contraceptives and migraine headaches as risk factors for stroke in a population of young women.

Investigations supported by NINDS have done much to elucidate the pathophysiology of migraine and have laid the groundwork for therapeutic advances such as the recent introduction of a new injectable agent, the serotonin-receptor agonist, sumatriptan

## **Initiatives**

## Ongoing Program Announcements (PA) Relevant to Women's Health, Issued Before 1993

- Role of Hormones in Epilepsy
  Even though there is a large and ever
  increasing amount of information on
  endocrine-brain relationships, the role of
  hormones in epilepsy is not well defined.
  The research goals of this PA focus on the
  basic neurophysiology and endocrinology
  involved in the proconvulsant or anticonvulsant activity of hormones, as well as
  the influence of seizure activity on
  hormonal states.
- Stroke in Blacks, Other Minorities, and Women
   Factors relating to the etiology, prevention,

early diagnosis, and treatment of stroke, including rehabilitation, as related to blacks, other minorities, and women will be examined.

## Program Announcements Relevant to Women's Health in 1993

- Neurological Basis of Recurrent Headache, Especially Migraine Areas of research related to the etiology, prevention, and treatment of recurrent headache, especially migraine, may include the elucidation of cellular and molecular events that cause or lead to headaches, development of new interventions, identification of risk factors or events that predispose one to migraine, determination of possible genetic factors, and investigation of the role of hormones in migraine headache
- Multiple Sclerosis.
  Research to shed new light on the understanding of the cause, pathogenesis, diagnosis, and potential treatments for MS are the primary objectives of this PA. Among suggested topics of research are the genetic, hormonal, or other factors that render women particularly susceptible to MS.

## Workshop

In June 1994, NINDS and NICHD co-sponsored a workshop on Thyroid Hormones in Pregnancy. The workshop addressed the issue of consequences to fetal brain development resulting from various maternal or fetal thyroid function at 8 to 16 weeks gestational age Participants—pediatricians, endocrinologists, child neurologists, obstetricians, and basic scientists—reviewed current knowledge, identified areas needing further research, and developed testable hypotheses.

## National Institute of Nursing Research

In 1993, the National Center for Nursing Research was redesignated the National Institute of Nursing Research (NINR) by the National Institutes of Health Revitalization Act. The research supported by NINR primarily addresses questions and hypotheses that arise from the direct clinical care of patients and families by nurses. Nursing research includes studies relevant to the diagnosis and treatment of human responses to actual or potential health problems. As such, nursing research

includes both scientific inquiries into fundamental biomedical and behavioral processes relevant to nursing and research relating to nursing interventions in patient care.

The perspectives employed in the design and conduct of nursing research are multidisciplinary; the outcomes are either for short-term or eventual improvements in nursing practice to enhance disease prevention and promote recovery and maintenance of health. Nursing research considers biomedical, behavioral, and environmental factors that contribute to the causes, prevalence, amelioration, and remediation of illness and disability. A major thrust is the understanding of the biomedical and behavioral underpinning of problems and issues presented in the clinical practice of nursing.

Fifty-two percent of this country's population are women, yet vast knowledge gaps in women's health remain. Women's medical complaints are more than twice as likely as men's to be dismissed by physicians as psychosomatic. Ninety percent of women with breast cancer are eligible for lumpectomies, yet more than half will undergo mastectomies. These are just a few of the penetrating issues galvanizing the women's health movement. Nursing research is addressing women's health concerns by studying normal symptoms, rethinking present treatments, and developing ways to help women make well-informed choices about their own health.

## Accomplishments

#### **Breast Cancer Research**

NINR supports studies to improve women's knowledge and behavior concerning breast cancer prevention and detection. NINR also funds research that leads to effective nursing interventions to support and enhance treatment of women with breast cancer.

In 1994, NINR funded research designed to examine the psychosocial and clinical impacts of using gene-based diagnostic tests in families with heritable forms of breast, ovarian, and colon cancer to identify those individuals who are at increased risk for developing cancer and those who are not and to gather information needed to establish clinical protocols for the optimum use of risk assessment technologies in the future.

Because consumer and provider demands are anticipated to be high, NINR investigators will develop, implement, and evaluate a model informed consent process for genetic testing for breast cancer that integrates the perceptions of consumers and providers. The model will address both content and style of disclosure and counseling. The findings will have implications for the offering and use of genetic testing and for the development of informed consent guidelines. Results will also have cost implications related to medical training concerning offering and obtaining consent for predictive testing.

Nausea continues to be one of the most commonly experienced side effects of cancer chemotherapy. Nausea reduces the patient's tolerance of cancer treatment and thus the opportunity to push for maximum chances of disease cure or control. As many as three out of four chemotherapy patients experience nausea and vomiting despite the use of antiemetic drugs. Besides being intrinsically unpleasant, nausea can lead to further complications such as anorexia, dehydration, metabolic imbalance, and psychological problems such as depression.

NINR-supported research has contributed significantly to the understanding of the complex physiological mechanisms responsible for chemotherapy-induced nausea. During the most recent phase of this research, investigators showed the effectiveness of an easily reproducible behavioral intervention to reduce the incidence and severity of this serious side effect. This research also showed that there is substantial involvement of the parasympathetic branch of the autonomic nervous system in nausea development and expression. New data suggest that spectral analysis, a computer modeling program, can be successfully used to measure patient characteristics before treatment to enable clinicians to predict the subsequent occurrence of chemotherapy-induced nausea. Further refinement of this model will improve pharmacologic and behavioral control of this symptom and enhance quality of life and treatment outcomes for cancer patients in general and breast cancer survivors in particular.

#### Contraception/Reproductive Research

Adolescents are considered at high risk for developing problems in achieving the mothering role. Maternal role attainment is important because it influences the quality of motherchild interactions and the subsequent development of children. NINR investigators are determining the effects of unique early intervention

programs in which nurses help adolescents to gain knowledge about the mothering role, develop reciprocal mother-infant interactions, and strengthen maternal self-confidence.

The research team has developed standardized nursing care protocols (health-related behaviors, maternal role, family planning, life skills, and social support) for the public health nurses administering the early intervention programs. These protocols will facilitate future study replication. A finding with major potential significance is that approximately 50 percent of the subjects are scoring greater than 18 on the Center for Epidemiological Studies Depression Scale (CES-D) at intake, indicating depressive symptomatology and possible clinical depression. The failure of adolescents to attain the maternal role may lead to serious developmental sequelae in their children Health promotion of adolescent mothers and their children is imperative

#### Estrogen Replacement Research

Only 10 percent of women in NINR-funded research said that the clinician should make the decision about hormone replacement therapy (HRT). Research indicates that 20 to 30 percent of women in selected studies failed to fill their HRT prescriptions because they were not fully convinced of the benefits or safety of the therapy. Clinicians develop relationships with patients and attempt to influence patients' adherence to their clinical advice, frequently without knowledge of exogenous factors that influence compliance with the advice given.

There can be no greater waste in health care than the consumer who takes time to access the system, invests money and time in a visit, but derives no outcome related to knowledge or behavior. If the moral, ethical, and professional arguments for including women as participants in decisionmaking about HRT are not compelling, perhaps the cost factor would provide sufficient motivation.

The lack of attention to the symptoms and health effects of menopause has resulted in frustration and dissatisfaction among women health care consumers. Current and previous research projects from the "Decision Making in Menopause Study" use intentional strategies to educate women and improve their understanding and memory related to menopause and HRT. This intervention study is intended

to enable women to make decisions that are consistent with their values and direct their behavior.

### Pregnancy Research

The United States currently ranks 20th in infant mortality among industrialized countries due largely to its high low-birth-weight (LBW) rate. Home-visiting of pregnant women at risk for I BW has been advocated by several national groups to augment routine prenatal care and improve maternal and infant outcomes. Such additive care could increase health care costs unless clearly improved patient outcomes are realized NINR investigators are examining the quality and financial benefits of modified prenatal care. Using a model of transitional health eare, NINR investigators are comparing maternal and infant outcomes and cost of care for pregnant women at high risk of delivering LBW infants. Women in the active intervention. group will receive half of their prenatal care from nurse specialists via home visits and telephone contact. This study is in its first year of

In a recently completed study, investigators used the transitional health care model to permit earlier hospital discharge. The investigators substituted a portion of hospital care with a comprehensive program of home follow-up care by nurse specialists. Three groups of women were prepared for earlier discharge, scheduled for home visits, and assisted by 24-hour on-call nurse specialists. Compared with control groups, cost savings were 29 percent for women who had cesarean sections, 38 percent for diabetic mothers with newborns; and 6 percent for women undergoing hysterectomies

Other NINR-supported research, using targeted telephone support intervention during pregnancy, has demonstrated a reduction in the incidence of LBW babies among low-income African-American women who are at risk for premature labor. In this program, nurse-initiated telephone calls (two to four per week) are scheduled for client convenience. In addition, the women may also contact the nurses on beepers at any time. This intervention study provides both an opportunity for frequent reinforcement of health education efforts and also a means to provide responses to client concerns and questions that may otherwise get lost between routine health care visits. This intervention is a cost-effective way of making

clinical expertise available to these women on a regular and as-needed basis to help them to accurately monitor their pregnancy for early signs of premature labor.

In another NINR-supported study, a culturally sensitive prenatal care program is being tested to improve maternal health and prevent poor pregnancy outcomes in Hawaiian, Japanese, and Filipino women. The content of the prenatal program has been designed to incorporate culturally specific information identified during focus groups and requested by the women of these three ethnic groups. In addition, strong community networks have been developed through neighborhood women's groups to provide additional support systems for these women.

### Heart Disease Research

Cardiovascular disease is the leading cause of death in women in the United States and is responsible for the hospitalization of 2.5 million women each year. NINR is supporting a clinical intervention study to (1) improve functional status and diet adherence, and (2) determine predictors of recovery after coronary artery bypass graft surgery in women. The special nursing intervention will consist of instruction and goal-setting for self-care, provision of information and question answering sessions regarding symptoms and symptom management, and reinforcement, encouragement, and support. This study is in its third year of funding and is especially timely because until recently women were excluded from most of the clinical trials for prevention and treatment of heart disease.

### Obesity/Eating Disorders

More than 24 percent of women in the United States are overweight, and obesity is more prevalent in vulnerable groups such as Black and Hispanic women. In a 5-year NINRsupported cross-ethnic community-based study, investigators are exploring weight management experiences and factors that influence the selection, use and success of the methods. Preliminary results indicate six major causes of overweight: (1) natal family norms (patterns of eating and activity learned while growing up); (2) heredity; (3) adult lifestyle (patterns of eating, activity and lack of time for exercise and meal planning); (4) life stresses (daily hassles); (5) emotional problems (longstanding psychological difficulties); and

(6) life transitions (major life events such as pregnancy or marriage). Adult lifestyle and life stresses were identified by most participants as the major reasons for weight gain.

#### Research on Women as Care Givers

Families provide more than three-fourths of the care giving of the older community-dwelling population. Usually, the women in these families serve as the primary care givers, with men helping in a secondary role. Care giving includes help with activities such as bathing, dressing, feeding, managing finances, obtaining medical care, cooking, cleaning, shopping, and transportation. As the burdens grow for families and care givers, particularly women, good matches between formal and informal providers and patients become more significant.

Level of frailty, settings in which care is provided, history of illness, and provider beliefs about the nature of long-term care influence both the care provided and the patient's perception of the characteristics of good and poor quality care. Preliminary research results indicate that differing conceptualizations by care givers, patients, and family members of what is meant by patient autonomy and quality care can create confusion, anger, and distrust.

Early data analysis has also revealed that a good personal match between care givers and patients can have paradoxical consequences of diminishing quality and/or safety of the care provided. Other findings highlight (1) the nature of negotiations that occur between patient and care giver about how care will be provided and (2) how formal care givers deal with what they experience as dissonance between expectations of the patient and family and the conflict between past training and current instruction.

### Menstruation and Menopause Research

Although menopause is a universal phenomenon among women, there is considerable individual variation in the manifestation and severity of a variety of perimenopausal symptoms. These symptoms, which are poorly defined and understood, include musculoskeletal and gastrointestinal problems, fatigue, insomnia, weight gain, vasomotor instability (hot flashes), depression and mood swings, and changes in cognition, perception, and memory. They are further characterized by extensive overlap, the absence of clear

pathology, and no well-defined treatments. These symptoms, which may persist over many years and become permanent in old age, are often a major reason for women to seek health care, lose work time, and experience a decrease in their health-related quality of life. Lack of specific identifiable pathology often leads health care providers to label these symptoms as functional syndromes or psychosomatic disorders and to treat them with pharmacologic agents (e.g., sedatives or tranquilizers), often with debilitating side effects.

NINR investigators have speculated that endocrinologic and metabolic changes associated with the menopause interact with or accelerate events of normal aging to promote increased incidence of metabolic bone disease, heart disease, diabetes, hypertension, breast cancer, osteoarthritis, autoimmune disease, and menstrual bleeding disorders in midlife.

The primary purpose of an NINRsupported, 5-year, multisite (seven clinical sites) cooperative agreement is to determine whether menopause-related changes in hormones or menstrual cycle patterns are associated with changes in joints indicative of arthritis development, loss of bone density, and changes in body composition. Specifically, the study aims to (1) describe the natural history of change in menstrual cycle length. bleeding duration, and amount of bleeding and the association between menstrual cycle characteristics of the menopausal transition and change in reproductive hormone levels; (2) determine whether associations observed in African-American women differ from those in white women: (3) describe the amount of bone change and body composition change across the menopausal transition in both groups using menstrual cycle patterns and hormone levels as markers: (4) describe changes in biochemical markers of bone metabolism, osteocalcin, and N-teleopeptides; and (5) ascertain whether the changes in bone density or bleeding patterns can be attributed to the menopausal transition after considering confounding and interaction effects of age, race, diet, body composition, or smoking. This study is in its first year of funding, and results are not available.

NINR is also supporting menstruation and menopause research that explores relationships between stress and endocrine dynamics.

Other research tests hypotheses regarding the hypothalamic-pituitary-ovarian axis and the etiology of psychoemotional and physical symptoms trained to the menstrual cycle. These studies should extend knowledge and lead to a better understanding of the adaptational responses to menstruation in a variety of understudied women's health clients.

#### Arthritis

Another NINR study addresses the applicability and effectiveness of an efficacy-enhancing arthritis self-management program for Spanishspeaking populations. To date, the research team has translated and revalidated Spanish arthritis specific scales and scales to determine general health for five diverse Spanish-speaking arthritis populations. The research team has determined that the most effective and efficient method of collecting data from Spanish-speaking individuals is by telephone interviews. The research team learned that the use of the telephone interview was just as effective and efficient a method of data collection as use of the home interview method. The research team is currently successfully randomizing 200 individuals to the program or to the control group. This program for Spanish-speaking populations will contribute to the health care field by providing a low-cost, community-based patient education program

In another NINR-supported study, the immediate and long-term effectiveness of a supervised exercise program is being evaluated on how it improves important daily functions of a group of rural, sedentary older adults with symptomatic arthritis of the weight-bearing joints. This intervention is a 16-week training program designed to increase the strength, flexibility, aerobic capacity, and speed of task completion of the participating elders and increase their knowledge about, acceptance of, and support for exercise. The study is primarily focused on how these elderly individuals with symptomatic arthritis maintain their fitness, exercise, and activity level after the supervised program has been completed.

Preliminary data from the study confirms the belief that even frail, sedentary, older adults with substantial chronic illness can be helped to become more active and independent in their function and to experience increased self-esteem and quality of life.

#### AIDS/STD Research

The millions of Americans who are living with HIV infection face a current or anticipated loss of immune function and the consequent development of opportunistic infections and/ or malignancies that may eventually affect nearly all organ systems. Care of these persons requires efforts to forestall the immune system breakdown and to cope with the multi-system effects, and often synergistic, clinical problems that are the result of the HIV infection and its treatment.

NINR is supporting a study examining sexual risk behaviors of minority, inner-city women of childbearing age. Already there are early signs of success in reaching this population with an impressive 98 percent retention rate for participants in the first year.

The Division of Intramural Research (DIR) is laying the foundation for interventions to alleviate symptoms and improve the quality of life for AIDS patients. DIR is currently conducting symptom management studies involving (1) a description of the nature, extent, and impact of nutrition-related changes during HIV treatment; (2) an examination of the nature and impact of antiretroviral drug therapy on muscle; and (3) a study of the nature and impact of fatigue on persons during HIV treatment. A number of substudies are also underway. Additionally, the biophysiological and psychosocial predictors of quality of life in individuals during treatment for HIV infection are currently being developed.

#### **Initiatives**

## Request for Applications (RFA)

• Studies of Genetic Testing and Counseling for Heritable Breast, Ovarian and Colon Cancer Risks (RFA-HG-94-001)

The collaborating organizations for this RFA were the National Center for Human Genome Research, National Cancer Institute, National Institute of Mental Health, and the National Institute of Nursing Research. The goal of the RFA was to solicit projects designed to examine the psychosocial and clinical impact of using gene-based diagnostic tests in families with heritable forms of breast, ovarian, and colon cancer to identify those individuals who have an increased risk of developing cancer and

those who do not and to gather information needed to establish clinical protocols for the optimum use of these risk assessment technologies in the future.

## Menopause and Health in Aging Women (RFA-AG/NR-94-002)

The collaborating organizations for this RFA were the National Institute on Aging, the National Institute of Nursing Research, and the Office of Research on Women's Health. The goal of the RFA is to stimulate comprehensive multidisciplinary research into the natural history of the menopause and the effect of the perimenopausal transition on women's aging and subsequent susceptibility to disease. Special emphasis is placed on minority populations because the menopausal experience in minority women has been particularly neglected and the unique biological and sociocultural factors that may differentially influence the menopausal transition and its consequences need exploring.

## Program Announcements (PA)

 Decisionmaking Processes in Women's Health (PA-NR/HS-95-020)

The collaborating organizations for this program announcement (PA) were the National Institute of Nursing Research, Office of Research on Women's Health, and the Agency for Health Care Policy and Research. The purpose of this PA is to study the treatment and intervention decisionmaking processes associated with noncancerous health problems of women that frequently result in the surgical procedure hysterectomy. These health problems have symptoms that may lead to a decision for hysterectomy even when the underlying pathology is limited. These problems include dysfunctional uterine bleeding, leiomyota (fibroids), endometriosis, pelvic pain, and uterine prolapse.

## Workshop

Directions for Menopause Research
 This workshop was co-sponsored with the
 National Institute on Aging, the Office of
 Research on Women's Health, and the
 American Menopause Society.

## NATIONAL INSTITUTE ON AGING

The National Institute on Aging (NIA) conducts research on the physiological and behavioral changes that characterize the transition from pre- to post-menopause, and on the diseases and disorders related to aging and decreased functional status. Research emphasis is on cancer, osteoporosis, hip fracture, urinary incontinence, and care-giving issues

## Disability and Disease in Older Women

The Women's Health and Aging Study is a prospective study of a sample of 1,000 older community-dwelling women with moderate to severe disability. Data are being collected on nearly 20 major diseases and conditions to ascertain their presence, severity, and impact on disability.

The NIA Epidemiology, Demography, and Biometry Program and the National Cancer Institute (NCI) Surveillance Program are conducting two studies that will expand the knowledge base on cancer in older women Tumors of the breast, ovary, and colon are a special focus because of their severity, especially for women 65 years and older

#### Menopause

The Baltimore Longitudinal Study on Aging (BLSA) involves measurements of bone mineral density at 6-month intervals and body composition and blood hormone levels (sex and growth hormones) at 3-month intervals. Another major study, the BLSA Vascular Initiative, is measuring arterial stiffness and cardiac structure and function to ascertain the cause of the dramatic rise in the incidence of hypertension, heart attacks, and strokes in women after menopause

The Menopause and Health in Aging Women trial will recruit 4,000 women, at least half of whom will be from African-American, Hispanic, and Asian-American populations. Cooperative agreements were awarded to seven chinical sites in Fiscal Year 1994. Studies will (1) characterize biological and psychosocial antecedents and sequelae of the menopausal transition, (2) examine effects of this transition on subsequent health and risk factors for age-related diseases, and (3) identify factors leading to the high utilization of hysterectomies in the perimenopause.

#### Physical Frailty/Osteoporosis

The NIA's Frailty and Injuries: Cooperative Studies of Intervention Techniques program consists of eight clinical studies testing inter-

ventions to prevent falls and maintain physical abilities in older persons by improving strength, balance, and endurance. Additionally, five chinical trials—STOP-IT. Sites Testing Osteoporosis Prevention Intervention/I reatments)—are exploring mechanisms underlying bone loss and responses of older persons to treatment.

## Accomplishments

## NIA/NCI Seer Collaborative Study: Comorbidity and Early Diagnosis of Cancer in the Elderly

The NIA Epidemiology, Demography, and Biometry (EDB) Program and the NCI Surveillance Program have combined their resources to address the high rates of breast cancer (incidence rates of more than 400 per 100,000 in women 65 years and older) and colon cancer (incidence rates of more than 330 per 100,000 in the 75 and older age group), and the problems of ovarian cancer for older women (62 percent of ovarian cancer mortality occurs in women 65 years and older) in two special studies. Other tumors that affect older women (e.g., urinary bladder, stomach, and cervix) are being investigated as well in a special study on comorbidity and cancer.

Supplemental studies have been added to the routine data collection activities of the NCI Surveillance, Epidemiology, and End Results (SEER) program, a population-based tumor registry. The SEER program will identify older patient's records and respondents for the NIAV NCI SEER Study on Comorbidity and Early Diagnosis of Cancer in the Elderly. The study addresses two major areas of mutual interest for specific tumors pertinent to women's health. They are (1) the existence of comorbid conditions and/or functional limitations at initial diagnosis of cancer, and (2) the response to signs and symptoms of cancer by older women in the presence of co-existing chronic diseases and physical limitations. Six of the seven tumors selected for the NIA/NCI SEER Collaborative Study for women are breast, ovary, cervix urinary bladder, stomach, colon. The study includes a focus for men on the tumors common to both genders as well as prostate cancer

Research questions include the following: (1) Are older women cancer patients more likely to have advanced stage disease at initial diagnosis of cancer? (2) How are concomitant diseases and/or illnesses (i.e., comorbidity) and the normal processes of aging associated with

cancer treatment in older patients? (3) What factors increase the length of time from recognition of symptoms to the time of diagnosis for older patient? and (4) What do older persons do in response to signs and symptoms of cancer (i.e., illness behavior)?

### Comorbidity

Data collection on approximately 7,600 patients for the comorbidity component of the NIA/ NCI/SEER Study was completed in late 1994 Six SEER geographic regions—Iowa; Utah; New Mexico; Atlanta, Georgia; Seattle, Washington; and San Francisco, California—participated in a record abstracting study. Data editing, entry, queries, and resolution have occurred. The final data file will soon be ready for analysis (April 1995).

#### Illness Behavior

The illness behavior component of the NIA/ NCI/SEER Study that includes interviewing approximately 800 breast, colon, and ovarian cancer patients in three age groups (55 to 64, 65 to 74, and 75 and older) will begin in May 1995. A pilot study to pretest the interview and study logistics will be completed in December 1994. Questions relate to symptoms prior to diagnosis, health actions, medical care and illness prior to the diagnosis of cancer, social support, quality of life, and functional status.

## Women and Disability: Women's Health and Aging Study (WHAS)

Women make up a majority of the older population and report higher rates of physical disability, spend more years in the disabled state, make up a substantially larger proportion of the nursing home population and have a greater need for formal and informal care than men. A number of important hypotheses related to disability and loss of independence in older women are being addressed by the NIA Women's Health and Aging Study.

The WHAS was initiated in July 1991 through a contract to The Johns Hopkins University School of Medicine. This 3-year prospective study of 1,000 older, community-dwelling women with moderate to severe disability aims to determine the effects and influences of diseases and other events on health status in women age 65 and older. Data will be collected on nearly 20 major diseases and conditions of aging—including cognitive impairments and mental illnesses—

to ascertain their presence, severity, and impact on disability. The women will be examined twice yearly to evaluate changes in disease and functional status, as well as hospitalization, nursing home admission, use of home health care, and mortality. A subset of participants will be studied intensively over a 6-month period, involving diaries of health and disability status and weekly contacts, to record information about transitional status between sources of care. The WHAS has completed extensive in-home examinations and participants are now in various stages of the follow-up process.

### Research on Menopause

Menopause and reduced or deficient ovarian function are increasingly believed to play a significant role in the etiology of short- and long-term disorders and diseases. Reduced ovarian hormone levels may play a key role in accelerated bone loss and osteoporosis and have been associated with cardiovascular disease and other disorders, such as urinary incontinence. Both osteoporosis and cardiovascular disease are major causes of frailty, serious disability, and mortality, and commonly lead to increased dependency and the need for care in nursing homes. Currently 1.3 million women become menopausal each year, and this number is steadily increasing. As they reach this landmark, women and their doctors are seeking accurate information about the significance of menopause on female aging and subsequent health in terms of the risks and benefits of long-term hormone therapy as it applies to the individual woman.

#### Baltimore Longitudinal Study of Aging

The BLSA is NIA's major intramural study of human aging. Established in 1958, the BLSA is America's longest-running scientific examination of human aging. The women's cohort of the BLSA was established in 1978. Studies are underway on (1) the gender similarities and differences in demographics, (2) the frequency of common diseases among men and women, (3) the drug treatment of these common diseases, (4) the differential effects on biological markers of natural versus artificially induced menopause, (5) the prevalence of urinary stress incontinence in women and its relationship to the aging process, and (6) the effects of estrogen on skin elastosis. This initiative includes the following subcomponents:

- The BLSA Perimenopausal Study
  This study monitors hormone activity in
  African-American and Caucasian women
  as they go through menopause by measuring bone mineral density at 6-month
  intervals and body composition and blood
  hormone levels (sex and growth hormones)
  at 3-month intervals. The research is examining age-associated losses in bone density
  and strength, changes in body composition,
  development of cardiovascular outcomes,
  and metabolic diseases. A separate intramural study is being conducted on the
  effects of estrogen replacement therapy on
  brain structure and cognitive function
- The BLSA Vascular Initiative
  This study measures arterial stiffness and cardiac structure and function to discover the cause of the dramatic rise in the incidence of hypertension, heart attacks, and strokes in women after menopause

Menopause and Health in Aging Women NIA issued an RFA in collaboration with the NIH Office of Research on Women's Health and the National Institute of Nursing Research titled, "Menopause and Health in Aging Women." As a result of the RFA, the Institute awarded cooperative agreements to seven clinical sites, a coordinating center, and a central laboratory in September 1994. The core protocol will generate information on menstrual cycle characteristics, markers of ovarian function, symptoms, demographics, health and social characteristics, sexuality, race/ethnicity, reproductive history, preexisting illness, physical activity and health practices, as well as risk factors for age-related disease, including osteoporosis, cardiovascular changes, body composition, and diabetes. One of the sites will identify factors leading to the high utilization of hysterectomies in perimenopause. The trial calls for recruiting 4,000 women in mid-life, at least half of whom will be from African-American, Hispanic, and Asian-American populations.

#### Menopause Research Advances

NIA supports a substantial ongoing grant portfolio on menopause, which includes basic molecular and cellular research on age-related changes in endocrine and ovarian function.

Recent research results include the following:

A study on hot flashes and core body temperature being conducted at Wayne State

University suggests that body temperature elevations may trigger the flash. Hot flashes are the most common symptom of the menopausal transition and affect a majority of women, although in varying frequency and severity. This study is the first to establish a link between core body temperature and hot flashes.

Researchers at the University of California, San Diego, have discovered that postmenopausal estrogen use may block adverse effects of thiazide diuretics in older women. Evidence from this study suggests that postmenopausal estrogen use masks thiazide-associated impairments in glucose tolerance and hyperinsulinemia. Modifications of most of the untoward metabolic effects of thiazides in women taking postmenopausal estrogen could provide a new incentive for the use of this traditional antihypertensive in elderly women

## Physical Frailty/Osteoporosis

The NIA supports clinical studies of age-related bone loss and fracture epidemiology, intervention trials to prevent or reverse bone loss, and studies of the effects of sex steroids and growth factors on bone cell function. The Institute also funds basic research on osteocyte biology and skeletal renewal and repair. In April 1994, NIA issued a PA to promote basic and clinical research on the effects of age on factors related to hone quality, skeletal fragility, and increased fracture susceptibility. In April 1994, NIA cosponsored a request for application (RFA) initiated by the National Institute of Arthritis and Musculoskeletal and Skin Diseases: Basic Osteoporosis New Experimental Strategies (BONES).

Five of seven clinical sites recently funded in response to the RFA on menopause described above will conduct prospective longitudinal studies to determine the differential contributions of age and ovarian hormone status to changes in bone mass as women approach and traverse menopause. Some studies will explore underlying mechanisms whereby menopause-related changes in the hormonal milieu accelerate bone remodeling and adversely impact bone mineral metabolism through dramatic increases in cytokine production or by interactions with factors related to vitamin D receptor polymorphisms

Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT)
NIA also supports research on the effects of exercise and other interventions on reduc-

ing the rates of falls. The Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT) program is a set of eight clinical studies testing the ability of interventions to prevent falls and maintain physical abilities in older persons by improving strength, balance, and endurance. FICSIT was initiated in April 1990, testing of interventions was completed in 1993, and the results are currently being analyzed. Analyses of results to date indicate that interventions can reduce fall rates and improve strength, balance, and endurance in frail older persons. An additional set of five clinical trials known as STOP-IT (Sites Testing Osteoporosis Prevention Intervention/ Treatments) is exploring the mechanisms underlying bone loss and the ability of older people to respond to treatment. Additional research will be pursued to determine the type and intensity of exercise that will yield the greatest benefit.

Research results from the FICSIT studies reported in the *New England Journal of Medicine* in 1994 indicate that falls in elderly persons can be significantly reduced by intervening against risk factors that produce falls, such as bone fragility and muscle weakness, postural hypotension, use of sedatives or multiple medications, and impairments of motion, such as balance and gait.

In 1994, a study of home-based interventions, including medication adjustments, education and training, and unsupervised exercise regimes, have produced reductions in fall rates of 30 percent in one study and 44 percent in another when compared to control subjects without interventions.

Controlled studies in frail nursing home residents found that a 10-week resistance exercise program approximately doubled leg strength, increased walking speed by 11 percent, improved stair-climbing power by 28 percent, and led to increased spontaneous physical activity, when compared with controls.

Several large clinical studies have confirmed that even modest amounts of regular exercise, equivalent to walking 30 minutes a day, can significantly improve health, prevent disease, and reduce the risk of death.

Although the total costs associated with falls are unknown, the yearly costs for acute care associated with fall-related fractures are estimated at \$10 billion. Approximately 30 percent of the community-dwelling elderly fall each year. In addition to being the sixth

leading cause of death among the elderly, nonfatal results of falls include physical injury, fear, functional deterioration, and institutionalization.

Prevention and Treatment of Osteoporosis Investigators at Stanford University have found that growth hormone administration decreases body fat and may prevent bone loss in older women. The study also found that recombinant human GH (rhGH) had no adverse affects on cardiovascular risk factors, such as cholesterol and blood pressure, and may actually lower low-density lipoprotein (LDL), at least in women not taking estrogen.

New epidemiologic findings from researchers at the University of California, San Diego, reinforce the importance of milk consumption for prevention of osteoporosis in older women. Regular milk consumption by women in youth and adulthood is associated with better bone mineral density in old age. Lifelong calcium intake appears to affect risk of osteoporosis both by contributing to peak bone mass around the age of 35 to 40 and by affecting the rate of bone loss thereafter. In contrast, investigators found a relationship between coffee consumption and lower bone density. This finding of a potential preventive effect of milk consumption on coffee-associated bone loss has broad public health implications, particularly for the large proportion of U.S. women estimated to consume inadequate dietary calcium intake.

Insulin-like growth factor I (IGF-I) was found to have potential in the treatment of osteoporosis. IGF-I stimulated bone formation in postmenopausal women. However, given the paucity of effective strategies to combat this disorder, long-term studies on the effects and the safety of low-dosage recombinant human IGF-I on bone mass in osteoporotic women are needed.

#### Asymptomatic Bacteriurea

Rates of asymptomatic bacteriuria (AB) range from 10 percent in community dwelling women to 25 percent and above in nursing home residents. Epidemiologic studies that showed AB to be associated with elevated death rates in older people raised the question of whether AB should be treated.

A randomized controlled trial in 358 older women (mean age 82) showed that antimicrobial treatment of AB was effective in eliminating AB, but had no significant effect on mortality. Eliminating treatment for AB

could result in considerable savings. Additional study findings from investigators at Harvard University suggest that the regular intake of cranberry juice beverage reduces the frequency of bacteriuria with pyuria in older women.

### Body Composition/Weight

NIA has issued a request for proposal for contracts to support an epidemiologic study. Dynamics of Health, Aging and Body Composition (HEALTH ABC). The primary objective of the study is to examine the incidence of physical disability in relation to weight-related health conditions and body composition in healthier older women. Change in body composition in old age, particularly loss of muscle mass and bone, may be a common pathway by which multiple diseases contribute to risk of disability. The reasons for changes in weight and body composition in old age and the influence of these changes on health outcomes are not fully understood.

Research in this areas has established an important link between heavier weight both in middle age and in old age and risk of loss of independence in ambulation in older women In 1994, the Journal of the American Medical Association published, "Body Mass Index, Weight Change and Risk of Mobility Disability in Middle-Aged and Older Women. The Epidemiologic Follow-Up Study of NHANES I " In addition, maintenance of stable weight may contribute to psychological well-being in women. NIA epidemiologists studying the association between weight change and psychological well-being in women have determined that recent weight gain was associated with poorer well-being in both overweight and nonoverweight women and recent weight loss with poorer well-being in nonoverweight women.

#### Burden of Care

Recent study findings suggest there is potential physical risk from assuming a care-giving role. A study conducted at Stanford University evaluated blood pressure and psychosocial responses to work and care-giving stress in a sample of women ages 50 to 65 years. Noncaregivers showed a drop in blood pressure that is typical when leaving the workplace to go to a nonwork setting, while care givers showed an increase in blood pressure responses when leaving work to go to a setting that involved the care receiver.

#### Initiatives

## Requests for Applications (RFA)

- The Role of Menopause in Women's Aging and Subsequent Disease (with the National Institute of Nursing Research) was designed to generate collaborative epidemiologic studies characterizing "the chronology of the biological and psychosocial antecedents and sequelae of the menopausal transition and effect of this transition on subsequent health and risk factors of age-related disease" (1994–RFA AG–94–002)
- Basic Osteoporosis New Experimental Strategies: BONES (co-sponsor, NIAMS primary) (1994–RFA)
- Planning Grants for Breast Cancer Research Programs in NCI-Designated Cancer Centers Two grant applications and several specific projects within the NCI Cancer Centers were funded in Fiscal Year 1994 that relate directly to breast cancer in aged women (1994–RFA CA/ES/AG 94-05)

## Request for Proposals (RFP)

• Dynamics of Health, Aging, and Body Composition (Health ABC) Field Center Proposed study will examine the incidence of physical disability in relation to body composition and weight-related health conditions in healthier older persons. (1994–REP: NIH–AG–95–04)

#### Program Announcements (PA)

• Biology of the Menopause:
Change of Ovarian Function
This announcement will support research to elucidate the molecular and cellular mechanisms of the menopausal process. It will address age- and menopause-related changes in the pituitary-ovarian axis in an attempt to understand the biological processes involved in the change in ovarian function across the menopausal transition, using appropriate animal models, human cells, or tissue specimens. (1994–PA)

Aging and Bone Quality
 This announcement will promote basic and clinical research to identify and

evaluate the effects of age on factors related to bone quality and/or to develop strategies to modify the impact of these factors on skeletal fragility and increased fracture susceptibility. (1994–PA–94–052)

### Conferences and Workshops

### Directions for Research on the Menopause (1993)

Conference to define the status of current scientific and medical knowledge on menopause, to identify deficiencies in understanding and in the technology and methodology necessary to study menopause and the menopausal transition, and to formulate promising areas for future research.

### • Self-Care in Later Life (1993)

Conference to review findings related to self-care and to recommend a research agenda in this area. Particular attention was paid to the special needs of older, frail women and gender differences in use of self-care strategies for enhancing health and functioning.

Human Models of Skeletal Aging (1994)
 National Institute on Aging/National
 Institute of Dental Research workshop
 to identify and validate models that more
 faithfully emulate age-related changes and
 pathophysiological processes occurring in
 the mature and elderly skeleton.

# • Third International Symposium on Osteoporosis (1994)

Co-sponsored by the National Institute on Aging, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Dental Research and the National Osteoporosis Foundation. The symposium was designed for basic and clinical investigators, physicians and other health care professionals and policymakers. Its objectives were (1) to disseminate new information ranging from biomedical research advances to the most current clinical management strategies on osteoporosis, and (2) to determine future research directions relating to the pathogenesis, diagnosis, and treatment of osteoporosis.

### Physical Functional Independence in Older Persons (1994)

Workshop to explore whether interventions against physical frailty could demonstrably maintain or restore independence, as measured by "hard" outcomes such as nursing home admissions or deficits in activities of daily living.

### NIA/NCI/AHCPR Working Group on Pharmacology in Aging and Cancer (1994)

A working group of geriatricians and medical oncologists was convened to address unique aspects of treating older-age cancer patients, including pharmacokinetics and pharmacodynamics of the aged considering cancer and comorbid diseases concomitantly.

# NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) conducts research to improve the treatment and prevention of alcoholism and alcohol-related problems. Alcohol abuse and alcoholism exact tolls of approximately \$98.6 billion each year—yet only a fraction, \$10.5 billion, is devoted directly to treatment for alcoholism, alcohol abuse, and subsequent medical consequences. The remainder can be attributed to lost productivity, excess illness, and early death. Alcohol claimed more than 108,000 lives in 1989—double the number lost to AIDS—while years of potential life lost to alcohol-related diseases exceeded years lost to heart disease and approached the years lost to cancer. Our health care system registers the repercussions: 20 to 40 percent of patients in urban hospital beds suffer from the effects of drinking regardless of the conditions that initiated their hospitalizations. Among the estimated 13.8 million people in the United States who are alcohol abusers or alcoholic, nearly 4 million are women. Although studies conducted primarily with men have provided much of our knowledge about alcoholism, recent studies involving more women are revealing that prevalence, age at onset, clinical features, and course and outcome of alcohol problems can be different between the genders.

### Accomplishments

# Genetics Plays a Key Role in Alcoholism in Women

Past research has demonstrated a strong hereditary component to alcoholism in men, but not in women NIAAA-supported researchers, analyzing data from the Australian and Virginia Twin registries, have confirmed significant genetic influence on the risk of problem drinking in women as well as men Based on these findings, NIAAA will expand the scope of family, adoption, and twin studies of women in the search for global measures of women's risk for developing alcoholism, insight into the mechanisms underlying the transmission of alcoholism through generations, and genetic markers that signal increased risk for alcoholism in women. Other research found that college-age, biological offspring of alcoholies can be differentiated from control individuals on a wide range of variables including personality, drinking motivation, alcohol use/abuse/dependence, verbal ability, academic achievement, and a range of psychopathology. These differences were similar for both men and women. Contrary to expectation, when gender by family history effects were found, greater family history effects were demonstrated for women

### NIAAA Fields State-of-the-Art National Alcohol Survey

In Fiscal Year 1993, NIAAA fielded the National Longitudinal Alcohol Epidemiologic Survey (NLAES), the largest and most indepth alcohol epidemiologic survey of the general population ever conducted in the United States, in which 42,862 respondents age 18 and older participated in direct face-to-face interviews. This survey, conducted by the Bureau of the Census through an interagency agreement, is designed to (1) estimate the size and characteristics of populations of people who consume alcohol, including abusers and dependent persons; (2) measure the number of individuals in need of but not currently receiving treatment for alcohol abuse and/or associated disabilities; and (3) provide information concerning access and barriers to alcohol-related treatment services, particularly among lowincome groups, women, and minorities.

### Alcohol Is a Critical Factor in Violence Against Women

The NIAAA has a multidisciplinary research program on alcohol and violence that includes studies focused on partner violence. These studies use cross-sectional, longitudinal, and experimental designs and draw on samples that include both large cross-sections of communities and special populations. Partner violence is being studied through extramural grants and an important intramural research project. The Institute also published NIAAA Research Monograph No. 24, Alcohol and Interpersonal Violence, which includes papers on partner violence. Not only is alcohol an antecedent to episodes of violence against women, but also physical or sexual violence against women appears to contribute to the onset of alcoholism. Recent NIAAA-supported research on frequent heavy drinking and marital violence among newlyweds has found that men who respond to conflict with angry withdrawal. and who believe that alcohol excuses aggression, are most likely to participate in alcohol-related physical aggression toward their spouses

# Psychobiology of Alcoholism May Differ in Women

Women experience significantly higher blood levels after identical doses of alcohol per kilogram of body weight compared to men. Women alcoholics have similar amounts of brain shrinkage compared to male alcoholics, as measured by computerized tomography, but with significantly shorter alcohol exposure histories. These differences highlight the need to study alcoholism specifically in women. In males, m-chlorophenylpiperazine (m-CPP) gives rise to a "high" and an "urge to drink" in approximately 40 percent of the Type II alcoholics, but rarely in Type I alcoholics. NIAAA intramural scientists are investigating effects of m-CPP in female alcoholics. In results to date, m-CPP has been administered in a double-blinded fashion to eight women alcoholics and two controls. Behaviorally, the women described mild anxiety symptoms similar to those described by Type I male alcoholics. Only one woman described an urge to drink that has been described by approximately 40 percent of the Type II male alcoholics. By comparing parameters related to scrotonin function in men and women, new insights into the pathogenesis of alcoholism in women will be gained

# Drinking During Pregnancy Continues To Be a Serious Problem

Research reveals that awareness of alcohol warning labels has contributed to a reduction of alcohol use during the third trimester of pregnancy, but not among the heaviest drinkers. Primary prevention for women of childbearing age and pregnant women is important. A crucial step in preventing alcohol-induced birth defects is identifying women whose drinking places them at increased risk for having children with fetal alcohol syndrome and related conditions. Currently, women with high-risk drinking patterns often are not recognized in clinical settings. Research to develop improved screening approaches will facilitate the identification of these women in primary care settings, in family practice units, and in obstetric and gynecological practices. Researchers are also working to develop brief interventions that can modify high-risk drinking. A hospital study of pregnant women seeks to improve the identification and treatment of alcoholabusing women through administration of a specially designed, brief screening instrument; for women who screen positive for alcohol abuse/dependence, a randomized, controlled trial will test the effectiveness of a brief intervention.

### NIAAA Receives Fiscal Year 1993 Women's Health Supplements

In Fiscal Year 1993, seven NIAAA grantees were awarded women's health supplements from the NIH Office of Research on Women's Health. These supplemental funds supported work to (1) collect information on childhood physical/sexual abuse among the women in a study sample in order to examine the relationship between early abuse and subsequent development of alcohol problems; (2) revise, refine, and pilot test behavioral treatment manuals (as used in the parent study) to fit female-index cases and to pilot test novel recruitment strategies to bring women alcoholics and their spouses into treatment; (3) develop a valid screening instrument to detect and diagnose trauma-associated psychopathology in alcoholic women. A secondary goal of this project will be to use the instrument developed to identify subgroups of alcohol-dependent women diagnosed as having dissociative or posttraumatic stress disorders (PTSDs), to collect pilot data to assess their response to naltrexone in preventing alcohol relapse; and (4) explore

whether alcoholic women with posttraumatic stress disorder will have a differential response to treatment of their alcohol dependence when compared to women without PTSD and to also examine whether the opiate antagonist naloxone, when added to cognitive behavioral therapy, improves their response to treatment; (5) enhance recruitment of rural and minority women into an ongoing study of the effects of alcohol on postmenopausal women; (6) examine gender-related differences in alcohol elimination rates due to aldehyde dehydrogenases; and (7) assess factors and relationships unique to rural female adolescent alcohol use.

# National Longitudinal Study of Women's Drinking and Problems Receives MERIT Extension

In Fiscal Year 1994, the Problem Drinking in Women: A National Longitudinal Study entered the MERIT extension phase. This study, which began in 1981, is the largest, most indepth longitudinal study of women's drinking conducted in the United States to date. Analyses of earlier waves of data revealed that indicators of the onset of problem drinking in women include nontraditional lifestyle, low self-esteem, history of childhood sexual abuse, and prior experience with drugs other than alcohol. The extension will include continued data analysis, a 1996 follow-up, and the addition of an international component to examine cross-national influences of family and work environment on women's drinking.

# Alcohol Consumption May Increase the Risk of Breast Cancer

Each year more than 150,000 new cases of breast cancer are diagnosed, and nearly 50,000 women die from this disease. Although most evidence suggests an increased risk for certain cancers only among the heaviest drinkers, moderate drinking may be related to female breast cancer. In one study, breast cancer was approximately 50 percent more likely to develop in women who consumed three to nine drinks per week than in women who drank fewer than three drinks per week. This indicates consumption at a level even lower than the one drink per day, which is often considered moderate for women. The effect of alcohol also appears to be dose-dependent, i.e., alcohol poses greater risk as doses increase. NIAAA has an ongoing breast cancer study using an animal model. Thus far, the findings

strongly indicate a linkage between ethanol and breast cancer. The results identify a cellular mechanism for ethanol-induced carcinogenesis in the rat mammary gland ethanol may increase the number and rate of cell proliferation of the terminal-end bud structures, which are known targets of chemical carcinogens and in which tumors have been produced.

### Progress Made in Efforts Against Drinking During Pregnancy

Education that has occurred over the last two decades has increased knowledge that alcohol is a teratogen and has had an impact on the drinking behavior of many pregnant women Many women still drink in a risk provoking manner in pregnancy, and research can inform us of what can be done to effect this behavior Health education activities, such as media education campaigns, the Surgeon General's advisory, warning signs, and the bottle label have helped to increase knowledge on letal alcohol syndrome and alcohol-related birth defects. Ninety-two percent of women know that alcohol can be harmful in pregnancy. How ever, their understanding of the risk is limited only 30 percent appear to understand that fetal alcohol syndrome is a life-long birth defect, not a child born intoxicated. With respect to behavior, drinking during pregnancy has decreased among women in the low-risk categories, but not in the high-risk categories

An important research finding is that significant improvements in infant outcome can occur when women stop drinking, even in mid-pregnancy. This is especially true for the most serious manifestations of fetal alcohol syndrome and FAE, the brain function deficits in behavior and intellectual performance. Therefore, reaching pregnant women who drink is well worth the effort in and of itself. There is the added benefit as well of changing drinking behavior for the next pregnancy.

NIAAA-supported research has developed several excellent screening tools to identify risk drinkers in primary and obstetric care, such as the T-ACE and the TWEAK. As good as these instruments are, additional efforts to develop better tools, including potential biological markers, may yield even more effective approaches. In addition, screening instruments for at-risk drinking are of no use if they are not incorporated into clinical practice. Clinics and physicians' offices are busy enterprises, and

screening for alcohol problems does not appear to be uniformly undertaken. Research can demonstrate both the ease and importance of incorporating such procedures.

### Atypical Maternal Alcohol-Metabolizing Enzyme May Contribute to Fetal Damage

In heavy drinking women, the presence of a variant form of the alcohol metabolizing enzyme alcohol dehydrogenase (ADH) may lead to an increased rate of alcohol elimination and thus increase the formation of acetaldehyde an intermediate metabolite of alcohol. Acetaldehyde may be more toxic to the fetus than alcohol itself. Pregnant women with known ADH genotype are being recruited to a study that will evaluate ADH genotype and differences in alcohol metabolism as risk factors for alcohol-related birth defects.

# Alcohol Depletes Fatty Acids Critical to Brain Structure and Function

A clinical study of alcoholies has indicated that there is a loss of essential polyunsaturated fatty acids in their tissues and blood cells. Such losses are believed to be related to the tissue liver and brain. Alcohol is perhaps the only this may lead to the degeneration of neural It is known from animal studies that losses in essential fatty acids may be caused by either an insufficient diet or by alcohol itself, or by a combination of the two Recent results establish that an omega-3 fatty acid deficiency can be caused in mammals and in humans when the diet does not contain docosahexaenoic acid (DHA), the principal polyunsaturated fatty acid in the nervous system normally found in human milk. The consequences of this may be impaired memory and learning.

The loss of DHA subsequent to alcohol exposure has now been firmly established in experiments on large mammals. Adult cats exposed to a single intoxicating daily dose of alcohol for 6 months showed drastic losses of polyunsaturates in the liver and blood stream and significant losses of DHA in the brain and retina. Adult rhesus monkeys maintained on a diet containing reduced amounts of essential fatty acids for 15 months sustained a significant loss of brain DHA. When a separate group of

these animals was exposed to alcohol on an ad libitum basis, a further decline of brain DHA was observed. A loss of neural function was associated with the loss of DHA in the alcoholexposed groups, as shown by tests of the retina.

Infant formulas do not contain DHA and this may adversely affect nervous system development, particularly when other aspects of nutrition such as vitamin intake may be compromised. In case of poor maternal nutrition, where sufficient body stores of these lipids have not been transferred, this may lead to neurological deficits or a propensity for neurological illnesses. It is also hypothesized that alcoholic women may bear offspring with increased risk of neurological problems through this mechanism. In order to study this syndrome, a model of omega-3 fatty acid deficiency was developed by rearing rats on a formula that is inadequate in omega-3 essential fatty acids. Females reared on this regimen exhibited a 50 percent decline in brain DHA and their offspring suffered a 93 percent loss by day 10 of life. This model provides an excellent means of studying the consequences of neural DHA loss.

### Gender and Racial Differences Are Found in Alcohol Metabolism

In a laboratory setting, alcohol metabolism was assessed in African-American and Caucasian men and women. The genotype of specific alcohol metabolizing enzymes was also ascertained. Significant gender differences in alcohol metabolism were found in African-American men and women of the same genotype. African-American women had lower peak alcohol concentrations and reached zero blood-alcohol concentrations faster than men. The Caucasian sample had even higher alcohol elimination rates and reached zero blood-alcohol concentration even faster. Hence rates of alcohol elimination differ by genotype of alcoholmetabolizing enzymes, race, and gender.

### Researchers Follow Up Women DWI Offenders 5 Years After Screening

A controlled follow-up study is being conducted of a cohort of females who were driving while intoxicated (DWI) to test the following hypotheses: (1) Personality attributes and driving attitudes will be more potent factors than the presence of alcohol use disorders in predicting collisions, DWI recidivism, and moving violations among women and men;

(2) a higher proportion of women than men DWI offenders will have psychiatric symptoms, mental health disorders, alcohol use disorders, and psychiatric diagnoses; and (3) race and ethnicity will moderate the above relationships, specifically, Native Americans will have a higher prevalence of alcohol-related diagnoses and driving risk.

# Health Services RFAs Net Applications Focusing on Women's Health

In response to the Health Services Research RFA detailed under Fiscal Year 1994 initiatives. research was initiated on several issues in women's health, including women's use of alcoholism treatment services and how health care coverage effects their use of those services. In the past, Employee Assistance Programs have primarily been designed around the needs of men. Research funded under this RFA will develop, implement, and evaluate a workplace alcohol prevention and treatment program specifically targeted to women and minorities. Both outcome effectiveness and cost effectiveness will be assessed. Previous research conducted among largely male samples has found that behavioral marital therapy in combination with alcoholism treatment produces better outcomes than alcoholism treatment alone. Current research attempts to establish a similar finding among women by adding more women subjects to an ongoing NIAAA study.

# Project MATCH Meets Recruitment Goals for Women

The goal of Project MATCH is to develop valid and practical guidelines for assigning patients to treatment regimens particularly suited to their needs, since no one treatment approach has proven effective for all alcoholism patients. This multisite clinical trial is a cooperative agreement involving eight separate grants participating as clinical research units and one data coordinating center. Early in its planning, Project MATCH set goals for the recruitment of women and minorities, the overall goal set was 25 percent women and 20 percent minorities. Both goals were accomplished. This is exceptional and may well be the highest representation of women in any large-scale, tightly controlled clinical trial in alcoholism. This accomplishment is even more impressive when one considers that three out of five of the sites in the aftercare

arms are the Department of Veterans Affairs (VA) facilities, which typically attract primarily men. These arms have nevertheless achieved an impressive recruitment of women

The project thus presents the opportunity to study a large number of women (more than 400 of a total of more than 1.700 subjects) and address the many hitherto understudied gender-specific questions not possible in previous smaller studies. Analyses will be able to answer many questions concerning not only the potential for matching based on gender. but also many other questions about the occurrence, characteristics, and progression of the disease in women. Both primary and secondary hypotheses have been developed focusing on gender issues to clarify optimal treatment modalities for women, and a rich database for other descriptive and analytic questions of the nature, course, symptoms, and consequences of alcoholism for women will emerge. The study is now in its 6th year, which is an intensive data analysis phase

Effects of Naltrexone on Eating Behaviors in Alcoholic Women Are Being Studied NIAAA-supported research is studying the efficacy of naltrexone in the treatment of alcoholic women with and without eating disturbances. Naltrexone, an opioid antagonist, has recently been approved by the Food and Drug Administration for the treatment of alcoholism. The efficacy of naltrexone, however, has not been well established in women in addition, alcoholic women usually have a unique set of problems including high rates of disordered eating. Recent research has shown that opioid antagonists may be effective in reducing the frequency of binging in women

Gender-Based Differences in Relapse Are Being Studied

with eating disorders and altering the preferences for sweet and fatty foods

From the fall of 1991 through the winter of 1995, NIAAA is supporting three research and development contracts to replicate and extend Marlatt's taxonomy of relapse precipitants through prospective, 12-month follow-up studies. One of the sites supported under this project had as one of its aims the assessment of gender differences in precipitants of relapse. Analyses indicate no significant differences between men and women in types of relapse situations

and no differences in drinking behaviors surrounding the episode. The analyses do, however, indicate differences in other aspects of the immediate relapse situation that reflect differences in drinking patterns between men and women, i.e., negative effect, presence of others at first drink, and lack of confidence in avoiding future drinking in similar situations.

### NIAAA Receives Fiscal Year 1994 Women's Health Supplements

In Fiscal Year 1994 NIAAA received six women's health supplements from the NIH Office of Research on Women's Health. These awards support the following supplemental work to (1) increase recruitment among older, rural and minority women in a study of alcohol effects on postmenopausal women; (2) add a sample of lesbian women to a study examining the probabilities of drunk driving among people previously arrested for driving under the influence compared to the general public; (3) extend the placebo-controlled buspirone arm of the parent study to women for a treatment duration of 12 weeks followed by a 12-week nonmedication follow-up period; (4) extend the scope of factors examined among nunority teenage girls in work on adolescent alcohol use and high-risk sexual behavior, (5) increase the scope of variables to be examined among adolescent girls in work on alcohol, psychosocial factors, and adolescent development, and (6) add samples of female lymphocytes to research on alcohol, infection, and host response

### **Initiatives**

### Program Announcements (PA)

 Preventing Alcohol-Related Problems Among Ethnie Minorities

This program was designed to encourage prevention research focused on African Americans, Hispanic Americans, American Indians/Alaska Natives, and Asian Americans/Pacific Islanders, with the primary objective of expanding the limited information, especially about girls and women, available relating to prevention strategies that are effective for these populations. Research was also invited that would explore groups within these populations, especially women, who have been found to be at

elevated risk for specific types of alcohol problems. (AA–93–47)

### Research on Relationships Between Alcohol and Violence

The purpose of this PA was to encourage research in specific areas of interest, including (1) individual and environmental conditions under which alcohol and violence may be causally connected. (2) the sequential processes by which alcohol use may lead to violent behavior and vice versa, (3) the physiological and neural processes and mechanisms through which alcohol and violence are linked, (4) the behavioral consequences of alcoholrelated violence, and (5) tests of the effectiveness of prevention strategies designed to reduce or prevent alcoholrelated violence. Research providing information on the protection of women from violence and on preventive interventions for women was especially encouraged. (AA-93-095)

### Health Care Services for Persons With HIV Infection

This PA was issued jointly with the Agency for Health Care Policy and Research, National Institute on Alcohol Abuse and Alcoholism, National Institute of Mental Health, and National Institute on Drug Abuse (NIDA) to encourage grant applications focused on research related to health care for persons with AIDS and other HIV-related diseases. Women, especially ethnic minority women, are increasingly at risk for infection, and alcohol may be a factor in high-risk sexual behaviors. (AA–93–110)

### Health Services Research on Clinical Preventive Services

The staff of NIAAA collaborated with the Agency for Health Care Policy and Research to develop a PA. For this PA, NIAAA was particularly interested in the identification, screening, and prevention of alcohol-related problems in primary care settings. The special interests of NIAAA are related to alcohol use and the efficacy of such interventions as brief advice and other strategies to reduce problem drinking, with emphasis on the separate needs of men and women where appropriate. (PA–94–062)

### Requests for Applications (RFA)

- Biomedical and Behavioral Research on Alcohol and Women
   This RFA specifically addressed issues of women and alcohol. (AA–94–01)
- Biomedical and Behavioral Research on Alcohol and Youth
   This RFA invited research that would identify gender-specific risk-factors for alcohol misuse, the relationship of alcohol misuse to sexually transmitted diseases and unintended pregnancy, and gender differences in the effects of alcohol exposure among young people. (AA–94–02)
- Alcohol and Minorities: Biomedical and Behavioral Research
  This RFA emphasized the need for research among alcohol-using women, particularly in understudied populations such as African-American, Asian-American, American-Indian, and Hispanic women.

### Underdeveloped Areas of Alcohol Abuse Prevention Research

(AA - 94 - 03)

This RFA cited the need for research on prevention strategies for fetal alcohol syndrome and other alcohol-related birth defects, on ways that sellers of alcohol might play more effective roles in reducing drinking by pregnant women, and on genetic and environmental factors associated with fetal alcohol syndrome in African Americans and American Indians. Moreover, this RFA encouraged research on prevention of alcohol misuse among the elderly, a population increasingly female with advancing years. Investigators were also urged to develop and test counter advertising strategies that focus on ethnic groups subdivided by age and gender. (AA-94-04)

### Health Services Research on Alcohol-Related Health Problems

NIAAA requested applications specific to aspects of health services research, again with an emphasis on gender distinctions for such concerns as access, utilization, and appropriateness of interventions. One area of interest emphasized the question of the adequacy and appropriateness of treatment and prevention services directed at women,

youths, and minorities who were referred from driving-while-intoxicated programs (AA=94=05)

### Medications Development for Alcohol-Related Problems

NIAAA requested applications on all aspects of medications development with one area of interest being gender differences in responses to and effectiveness of medications. (RFA–94–06)

### Working Group

NIAAA convened a working group for Prevention Research on Women and Alcohol held September 13 to 14, 1993, in Bethesda, Maryland. A monograph presenting a state-of-the-art review of the papers generated from this conference will be published in Fiscal Year 1995.

# NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

The National Institute on Deafness and Other Communication Disorders (NIDCD) conducts and supports research and research training on normal mechanisms, as well as on diseases and disorders of hearing, balance, smell, taste, voice, speech, and language NIDCD also conducts and supports research and research training that are related to disease prevention and health promotion. NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The Institute supports efforts to create devices that substitute for lost and impaired sensory and communication functions.

### Accomplishments

A number of diseases, disorders, or conditions within the mission of NIDCD affect women disproportionately. Five examples have been selected for inclusion in this report. The remaining disorders may occur more often in men than in women.

### Spasmodic Dysphonia

A number of currently funded research projects examine spasmodic dysphonia, a neurogenic voice disorder with a higher prevalence in females, resulting from impaired laryngeal movement. Respiratory and laryngeal kinematic

and aerodynamic data are used to determine whether laryngeal and supralaryngeal electromyographic abnormalities are identifiable in kinematic and aerodynamic signals. This approach will be used to develop clinically applicable tasks and measures to determine the breadth and depth of vocal tract neuromotor disruptions in spasmodic dysphonia.

A complementary research project compares thyroarytenoid and posterior cricoarythenoid muscular activity during sustained voiced and voiceless speech sounds in unimpaired and spasmodic dysphonia subjects. In addition, this research is attempting to distinguish features of the two types of spasmodic dysphonia, adductor and abductor, at the level of neuromotor control. Results thus far suggest that a possible explanation for the heterogeneity of voice symptoms in spasmodic dysphonia is the relationship between disrupted neuromotor input to larvingeal muscles and compensations constrained by laryingeal biomechanics.

Extramural and intramural NIDCD scientists are examining the use of botulinum toxin injections for the treatment of spasmodic dysphonia Although previous work has indicated that bolutinum toxin is a safe and efficacious form of therapy, controversy has remained regarding the most efficacious dose and route of injection (unilateral versus bilateral). A double-blind, placebo-controlled study is ongoing to assess the efficacy of two dosage levels and the two techniques of injection. Findings will allow physicians to make appropriate recommendations for clinical care for this exceptionally disabling condition.

### Otosclerosis

Otosclerosis is the most common cause of progressive conductive hearing loss in adults and is more common in women than in men. Recent evidence suggests that a precipitating factor in this disease may be a subclinical viral infection, since viral antigens have been isolated from the bone overgrowths induced by the disease process An NIDCD-supported scientist is investigating the cellular and biochemical events leading to otosclerotic bone remodeling. Recent work has shown that drugs that inhibit prostaglandin synthesis are effective inhibitors of localized bone resorption. In addition, a new member of the biphosphonate class of drugs has also been shown to be a powerful inhibitor of bone resorption in vivo.

### Salt Taste

Hypertension is a well-established risk factor for cardiovascular disease, which is the most common cause of mortality among women. Hypertension occurs in approximately 27 percent of women but is specially common among postmenopausal African-American females in whom the incidence reaches approximately 80 percent. Extensive literature implicates excessive salt intake in the onset and maintenance of hypertension. NIDCD-supported scientists are evaluating various measures of salt taste for their potential in rapid screening for salt-sensitivity as determined by conventional means.

### Cytomegalovirus

Cytomegalovirus (CMV) is the leading cause of nonhereditary deafness. CMV is also recognized as the most common cause of human congenital infection, occurring in up to 2.5 percent of all live births. It is estimated that the sequelae of congenital infection may account for as many as 40,000 new cases of sensorineural hearing loss per year. Recent evidence suggests that pregnant women with acquired immunodeficiency syndrome (AIDS) are at greater risk for delivering children with congenital CMV infection and that their infected children are more vulnerable to CMV morbidity. However, the pathogenesis of congenital CMV infection, for both immunocompetent mothers and those with AIDS, is still poorly understood. The development of animal models has been hindered by the species-specific nature of the virus. Recently, NIDCD-supported investigators have been successful in establishing a guinea pig model of congenital CMV infection (GPCMV) in the auditory system, which closely resembles the neuropathophysiology and histopathology seen in human congenital infection. GPCMV thus provided the first experimental model system for congenital CMV-induced sensorineural hearing loss. These investigators are now adapting their current guinea pig protocol to create a model of AIDS-associated congenital CMV infection with immunosuppressed pregnant guinea pigs.

### Otoacoustic Emissions

The auditory system not only receives sounds from the outside environment but also, in its processes of sound analysis, actively produces sounds. These sounds are called otoacoustic emissions (OAEs) and are currently being studied

as phenomena yielding information on the integrity of both the normal and disordered auditory system. The prevalence of measurable OAEs is higher in women than in men. Because OAEs are correlated with gender and because gender is determined genetically, investigators, in an effort to address the long-standing question of the genetic contribution to OAEs, have collected OAE data on sets of twins (monozygotic females, monozygotic males, dizygotic females, and dizygotic males). A strong hereditary component has been found.

### Fluency Disorders

Stuttering is a speech disorder that typically begins in early childhood. Although it is estimated that more than 2 million Americans stutter, continuing research is needed regarding its cause, factors that determine its development over time, subtypes of stutterers, early detection, differential diagnosis, and treatment. Several studies that will have significant impact on these issues are currently in progress. One longitudinal project examines the onset and development of stuttering in early childhood. Results will provide critical information about the developmental trends of the disorder, factors that can be used for early identification of stuttering, differentiating subtypes of stutterers, and identifying children at risk for severe stuttering who are in need of early intervention.

Other current studies are developing a reliable method for measuring chronic stuttering and examining the occurrence in young children of stuttering with phonological (articulatory) disorders. Findings will help clarify the relationship between phonology and stuttering and identify perceptual and acoustic indexes of "typical" and "atypical" dysfluencies. Together these studies will provide important information on a variety of theoretical and therapeutic issues.

### Noise-Induced Hearing Loss

Noise-induced hearing loss represents the most common preventable form of hearing loss in the United States today. In an increasingly technical society, the sources of potentially harmful levels of noise have steadily increased over the years and with them the prevalence of noise-induced hearing loss. Some common noise sources include gunfire, power tools, heavy equipment, turbines, and engines.

There is widespread recognition that substantial individual variability exists in susceptibility

to the effect of noise, with males showing the greater prevalence in noise-induced hearing loss. There is no clear evidence, however, of a biological basis for the greater prevalence in males; rather, it appears that males have had greater occasion for ongoing exposure to potentially harmful noise sources in their military service, in the use of firearms, and in both recreational and occupational proximity to engine or machine noise. As employment opportunities become more equally available to both men and women, it is possible that this gender prevalence will change.

NIDCD has developed a campaign to educate third through sixth graders about high-risk noise activities and the biology of hearing. A videotape and a teacher's guide titled "I Love What I Hear" have been produced. Extramural research supported by NIDCD continue to address such critical issues as susceptibility to noise, determination of the mechanisms of acoustic injury, and the elucidation of the interaction of noise and aging.

### Smell

A predominant problem in the elderly is the natural decline in the sense of smell that typically occurs after age 60. Loss of the sense of smell can also be caused by exposure to some chemicals and by some medicines. A person with a faulty sense of smell is deprived of an early warning system that is typically taken for granted. The sense of smell alerts individuals to fires, poisonous fumes, leaking gas, and spoiled foods. In addition to a reduction in quality of life for those unable to smell, the loss of this sense can be associated with nutritional deficiencies in the elderly. Interest in and enthusiasm for eating are much reduced in those who cannot smell their food.

The loss of the sense of smell with age parallels the diminution of hearing and vision with age. Interestingly, females have a more acute sense of smell than males throughout the age span. NIDCD grantees developed a smell identification test that made it possible to test the sense of smell throughout the age span. It was this test that revealed that at all ages females have a more acute sense of smell than males. With this clinical tool, when patients complain of a loss of the sense of smell, their sense of smell can be measured and compared to what is normal for their age and gender. Examination of gender distributions revealed that a larger proportion of women than men

in the patient population evidenced upper respiratory infection-related chemosensory deficits, a greater proportion of male than female patients evidenced head trauma-related deficits, and the proportion of men and women with nasal sinus disease-related chemosensory deficits did not differ appreciably.

# NATIONAL INSTITUTE ON DRUG ABUSE

The National Institute on Drug Abuse (NIDA) supports a broad-based program of epidemiological, preclinical, prevention, and treatment research addressing drug abuse and women, as well as gender differences in drug abuse. The program focuses not only on addiction but on a variety of problems related to drug abuse, including, but not limited to, unwanted pregnancies, sexually transmitted diseases and AIDS, crime and violence, and childhood sexual abuse Furthermore, research has shown that it is imperative that we consider the prevention and treatment of drug abuse and addiction in women. within the added context of cultural and ethnic differences, particularly as they are reflected in male-female relationships. Much of NIDA's research on women and gender differences is centered in three research programs.

### Accomplishments

# Gender Differences in Cocaine Initiation and Abuse

In a study of cocaine use, approximately 90 percent of women reported that men played some role in their involvement with crack cocaine. By contrast, only 17 percent of men reported that women were involved in their initiating or maintaining the use of crack cocaine. Women were more likely to begin or maintain cocaine use in order to develop more intimate relationships, while men were more likely to use the drug with male friends and in relation to the drug trade. These data add to a growing body of literature suggesting the need for further study of gender factors in the initiation, maintenance, and treatment of drug abuse.

### Antecedents of Crack Cocaine Abuse Among African-American Women

A study of antecedents of crack cocaine abuse among African-American women found preexisting psychiatric problems to be a major co-factor. Specifically, researchers found a strong correlation between the age of first drug use and the first depressive episode. They also found that women who used crack cocaine reported being initiated into cocaine use by a male sex partner. In addition, these women had conflicting relationships with, and less attachment to, their mothers. Also, women with drug-using family members reported earlier illicit drug use. Specifically, crack use among women was significantly associated with alcohol use by their mothers. Approximately 46 percent of the women reported maternal alcoholism in contrast to 8 percent of men reporting maternal alcohol use in a companion study. Also, cocaine-using women frequently reported incidents of sexual abuse, currently and in their past. Of the 64 percent of the women who reported sexual abuse, twothirds reported that the abuse occurred before the age of 18.

# An Association Between Crime and Drug Abuse Among Women

NIDA research found that about 80 percent of women in residential or outpatient drug treatment programs had been crime victims. In addition, female crime victims were more likely to have major drug and alcohol problems than nonvictims. Female crime victims who suffered from posttraumatic stress disorder (PTSD) were almost 10 times more likely to have major alcohol problems and 17 times more likely to have major drug abuse problems than nonvictims. Numerous studies have shown PTSD to be a strong potential causative factor for substance abuse. NIDA scientists have also found substance-abusing parents to be more likely to perpetrate sexual or physical assault and to have children who are victimized.

### Drug Use Among Female Prisoners

NIDA has funded a study of women prisoners that focuses on drug abuse and other problem behaviors including HIV/AIDS risk behavior, violence, psychiatric disorders, and history of trauma. Many women in the study had been victims of psychological trauma, particularly from physical and sexual abuse. This study has provided important information on risk behaviors. Among the women there was a strong relationship between trauma and the characteristics of HIV/AIDS risk behaviors: any history of psychological trauma increased the risk and frequency of these high-risk

behaviors. However, sexual abuse, abuse at an early age, and abuse by a family member appeared to increase the frequency and severity of HIV/AIDS risk behaviors even more. NIDA researchers believe that this project may be the first to provide rigorous and systematic documentation of this relationship.

# The Role of Pregnancy and Parenting in Women's Drug Use

Pregnancy and mothering remain important aspects of life for many women addicts. In NIDA ethnographic studies, pregnant and postpartum women who used heroin, methamphetamine, or crack cocaine at least once a week during pregnancy admitted trying to reduce the risk for their fetuses. Drug-using pregnant women also reported problems dealing with authorities and stigma in their communities because of their drug use. Many women felt that health care providers were attempting to enforce moral requirements and "straight" society's views of proper behavior. The women indicated that, as an alternative to seeking medical or drug abuse treatment, they relied on the media as an information source about drugs that were most harmful to their fetuses and their own health. These women determined the need for prenatal care by weighing their belief in its value against the risks involved in obtaining or avoiding care. In a related study of 120 pregnant and postpartum addicts, 62.5 percent had been battered at least once in their lives, and 26 percent had been battered during pregnancy.

# HIV/AIDS Prevention Among Minority Women in Methadone Clinics

NIDA has been studying HIV/AIDS prevention among minority women in methadone clinics. One NIDA-funded study compared an experimental intervention that showed women how to teach their friends about HIV/AIDS, using a standard intervention that did not encourage women to disseminate this information. Researchers found greater reductions in highrisk sexual behaviors and significantly greater increases in self-esteem in the experimental group. The experimental group also reported engaging in significantly more AIDS prevention activities regarding the use of condoms and the sharing of intravenous drug needles. In addition, researchers found a greater reduction in reported illicit drug use in the experimental group; specifically, use dropped 16 percentage points (from 42 2 to 26.2 percent) compared to a drop of only 3.6 percentage points (35.7 to 32.1 percent) for the control group

Drugs and Female-Perpetrated Homicides Preliminary information on the drug-relatedness of female-perpetrated homicides in a cohort of 589 females convicted of homicide or manslaughter in the State of New York indicated that female-perpetrated homicide was more complex than its portrayal in the literature. Respondents killed various people in a variety of circumstances and for different reasons. Adult intimates, husbands, boyfriends, francees, and lemale lovers were the victims of only 20 percent of the homicides, and only 18 percent of the homicides were the direct consequences of an abusive situation. These results do not support the notion that most female-perpetrated homicides are due to

Drugs played a role in 42 percent of the homicides, a lower percentage than found for male-perpetrated homicides. Alcohol was involved in 57 percent of all the drug-related homicides, cocaine (in powdered form) and crack in about 25 percent, and heroin in about 18 percent. A particularly dramatic finding was that 88 percent of the women reported some type of physical or sexual abuse during childhood, and 90 percent experienced physical or sexual violence as an adult.

### Positive Adolescent Life Skills (PALS) Training for Teenage Women From Different Cultural Backgrounds

The weekly 16-session PALS training program is a therapeutic approach that combines cognitive and behavioral training to improve adolescents' ability to avoid drugs, alcohol, and unsafe sexual practices; to provide positive support to adolescents' families; and to restructure the adolescents' social networks to enhance the quality of their peer relationships.

In a study designed to evaluate the PALS training program, Latina adolescents appeared three times more likely to be using drugs after completing the non-culture-specific PALS program than were Anglo and African-American women. At pretreatment assessment, alcohol, marijuana, and tobacco were drugs of choice, although other drugs (e.g., cocaine, LSD, amphetamines, inhalants) were also used during the 3-month period before enrollment. Results indicated that the percentage of African-

American women reporting use of one or more other drugs declined significantly between intake and 3 months of posttreatment, whereas the percentage who reported the use of marijuana, alcohol, and tobacco declined only marginally, if at all. In contrast, no change was observed in substance use over the same period for the Latina adolescents. Posttreatment client interviews suggest that, to increase effectiveness, the social skills should conform more closely to the culturally determined values and expectations governing social interactions within the different cultural groups represented in the program.

# Treatment of Pregnant Women: "The Perinatal 20"

Pregnant women who abuse drugs are at risk of ectopic pregnancy, still birth, low weight gain during pregnancy, spontaneous abortion, risk of child neglect and abuse. To understand the issue of obstacles to treatment for women, NIDA has been studying treatment for women project. The Permatal 20, is examining the port services for pregnant women. In 20 sites nationwide. NID 1-sponsored researchers are testing the effectiveness of support and other pregnant women into treatment and helping them to stay there. The demonstration sites also provide medical and treatment services to study populations. Early findings suggest programs that address not only their drug abuse but also provide practical services to help meet their basic needs. These needs include food, clothing, shelter, thild care, transportation, medical care, and social support. Other important services include legal assistance, literacy training, parenting training, family therapy, and family planning services

### Intensive Outpatient Program Versus Residential Program for Pregnant Women Investigators have found that many, but not all, pregnant addicted women do as well in

an intensive outpatient program as in a residential program. Because the cost of a residential program many be three times that of an outpatient program, there is potential

for significant cost savings if a profile of those who do well in intensive outpatient care can be developed. Such a profile would permit assignment of these patients to the least costly modality able to provide effective treatment.

### Maternal Smoking

Investigators used information from two samples of mothers and firstborn adolescents for whom data on maternal smoking during and after pregnancy were available. They reported that maternal smoking during pregnancy, controlling for postnatal smoking, selectively increased the probability that female children will smoke and will persist in smoking. These preliminary findings raise the possibility that nicotine or other substances released by maternal smoking may affect the fetus, perhaps through the nicotinic input to the dopaminergic motivational system, so as to predispose the brain during a critical period of its development to the subsequent addictive influence of nicotine consumed more than a decade later in life. Further research is required to control for possible confounding factors.

National Pregnancy and Health Survey

In July 1994, NIDA completed the first nationally representative survey on the prevalence of drug use among pregnant women in the United States. The National Pregnancy and Health Survey provides, for the first time, a national estimate of the number of women who reported use of licit and illicit drugs during pregnancy and the number of infants born to them. The data, based on self-report (55 percent confirmed by randomized toxicology testing), were collected from 2,613 women who delivered babies in 52 hospitals from October 1992 through August 1993. Of the approximate 4 million women who deliver live-born children annually in the United States, 5.5 percent, or 221,000 women, are projected to have used some illicit drug during pregnancy (222,000 live births). The two most frequently used illicit drugs were marijuana (119,000 women, 2.9 percent) and cocaine (45,000 women, 1.1 percent). In terms of legal substances, an estimated 757,000 women (18.8 percent) used alcohol, and 820,000 women (20.4 percent) smoked cigarettes at some time during pregnancy. A strong link existed between cigarette and alcohol use and the use of illicit drugs. Only 6 percent of those who reported

no use of any illicit drug used alcohol and cigarettes during pregnancy. Conversely, of those women who reported no use of alcohol or cigarettes, only 0.2 percent used marijuana and 0.1 percent used cocaine. However, of those who used both alcohol and cigarettes, 20.4 percent used marijuana and 9.5 percent used cocaine.

Ethnic differences in estimated rates of substance use during pregnancy were significant: 11.3 percent of African-American women contrasted with 4.5 percent of white women and 4.4 percent of Hispanic women. However, in terms of numbers, more white women used illicit drugs during pregnancy (113,000) than African-American (75,000) and Hispanic (28,000) women. Differences in drug use did not occur in terms of age (5.7 percent of women under 25 years of age, 5.1 percent of women 25 to 29 years, and 5.5 percent of women 30 years or older), but differences did appear in terms of drugs used with marijuana more frequently among young women and cocaine use among older women. These data have tremendous public health implications for prevention and treatment programs.

HIV in Pregnant Women: The Women and Infants Transmission Study II (WITS II)

By means of a Memorandum of Understanding, NIDA and the National Institute of Allergy and Infectious Diseases (NIAID) formalized their collaborative research efforts on the impact of HIV infection in pregnant drug-using women and their offspring. NIDA will provide funding for one of the sites (Columbia University) of the NIAID-supported WITS II, a multicenter study of factors related to maternal-infant HIV transmission and to disease progression in the women and their infected children. NIDA funds will enable continued development of Columbia University as the core site for enhancing research on the drug-use-related aspects of the WITS II agenda and will allow for pregnant HIV-infected women, the majority of whom are drug users.

### HIV Perinatal Transmission and Birth Order

In a longitudinal project, risk of HIV infection was examined relative to a child's birth order following a mother's known HIV infection. Analyses to date suggest that in this sample a significantly higher risk for HIV infection was found for children born subsequent to the

birth of an older HIV-infected sibling than for those children born subsequent to the birth of an older, uninfected seroreverter. While additional information (e.g., stage of maternal disease progression) is critical for a conclusive interpretation of these results, the findings stimulate hypotheses with implications for research on mother-to-child transmission of HIV infection.

Prenatal Care for HIV-Infected Women In a study attempting to identify health care delivery and clinical factors related to risk of infection and rate of disease progression in children of HIV-infected mothers (e.g., methadone treatment, level of prenatal care for HIVinfected pregnant women, history of untreated maternal drug abuse, and mother's and child's antiretroviral and prophylactic drug treatment). analyses of more than 2,000 pregnancies have shown that very few HIV-infected women received adequate prenatal care (20 percent reported no prenatal care and an additional 45 percent reported too few visits). These findings have important implications for the translation of clinical findings into actual practice, i.e., clinical trial findings of a twothirds reduction in the rate of mother-to-infant HIV transmission by women treated with zidovudine during pregnancy (with short-term treatment of the infant after delivery). Results also showed that prenatal care was associated with reduced adverse birth outcomes (e.g., low birthweight and preterm birth). Further analyses will examine associations of health care patterns and clinical factors with the child's clinical course. This study includes the largest population of pregnant, HIV-infected women to be analyzed to date and constitutes the first detailed analysis of prenatal care to be conducted for this population.

### Mutant T-Cells in Pregnant Women

Researchers at the University of Texas Medical Branch, Galveston, demonstrated a more than threefold and more than twofold increase over nonsmoking pregnant women in mutations of the hypoxanthine phosphoribosyl transferase (hprt) gene in pregnant women who smoked marijuana and cigarettes, respectively, early in their pregnancies and before.

Rish for Seroconversion Among Women Recent analyses from an ongoing HIV seroincident cohort study demonstrated higher seroconversion rates among participants ≤35 years of age and among women, with the highest incidence of infection among younger women (3.17 per 100 person semesters at risk). Those participants who reported active drug injection in the 6 months during which seroconversion occurred were more likely to seroconvert than those not reporting active injection, with a relative incidence of 1.58. Among women, a history of three or more sexual partners was positively associated with seroconversion. Among men age <35, a sexually transmitted disease within the last 6 months, a lifetime history of syphilis, and current drug injection were significantly associated with seroconversion. These results suggest that sexual transmission is particularly important in infection in women, while drug-injection variables may be more important in infection in men. In the same study a comparative analysis of CD4 and CD8 levels in injecting drug users compared with homosexual men indicated that injecting drug users have significantly lower levels of CD4 and higher levels of CD8. Following seroconversion, larger changes in both CD4 and CD8 were observed in homosexual men as compared to injecting drug users, but after 2 years CD4 levels converged and then declined at similar rates in both groups.

### Behavior Interventions in HIV/AIDS Prevention

The Women Helping to Empower and Enhance Lives (WHEEL) project is a multisite pilot study of the role of behavior change in an HIV-prevention model for at-risk women who are sexual partners of injecting drug users. This NIDA-funded program was designed specifically to help women deal with such issues as family violence, empowerment to reduce the risk of HIV/AIDS, and independence. Through group sessions, women learn how to negotiate condom use with their sex partners and how to manage potentially negative consequences such as rejection and physical abuse.

Results indicated that AIDS knowledge among study participants increased significantly from baseline to follow-up and women reported being more comfortable talking with their main sex partner about using condoms. More important, women significantly reduced their sexual risks and drug use and increased their sense of control over their own lives. The proportion of women engaging in unpro-

tected sex went from 87 to 78 percent. At the initial interview, about 28 percent of the women reported using drugs before sex; in comparison, at follow-up only about 21 percent reported using drugs before sex. Women significantly decreased their overall drug use over the past 30 days, from 7.7 days to 6.5 days at follow-up. Although the data show significant increases in protected sexual behavior, the levels of sexual risk remain very high and more effective sexual behavior interventions are necessary.

### Technical Reviews

NIDA conducted the following technical reviews dealing with drug abuse and women:

- Drug Use and HIV Infection: Impact on Women and Children;
- Behaviors of Drug-Exposed Offspring;
- Women & HIV:
- Natural History/Longitudinal Studies of HIV in Drug Users;
- The Context of HIV Risk Among Drug Users and their Sexual Partners;
- Medications Development for Treatment of Pregnant Women;
- Methodological Issues: Etiology and Consequences of Drug Abuse Among Women:
- Biomechanisms and Perinatal Drug Exposure; and
- Perinatal 20.

These technical reviews served to assess the current status of research in these areas and to identify research gaps and new directions.

### **Initiatives**

### **Program Announcements**

 Etiology, Consequences, and Behavioral Pharmacology of Female Drug Abuse Although the number of male drug abusers and addicts exceeds that of females, the consequences of drug abuse by women are more severe. In addition, preliminary data from NIDA-supported research indicate that after initial use, women may proceed

more rapidly to drug abuse than men. This announcement seeks to stimulate research on the etiology and consequences of drug abuse by women of all ages and reproductive status and on gender differences in the behavioral effects of abused drugs. Studies on the etiology, natural history, and consequences of drug abuse unique to women include health risk. psychosocial, psychiatric, physiological, and neuroendocrine factors and clinical, social, economic, and legal issues related to the multiple roles and status of women (e.g., the role of drug use in female sexual activity, pregnancy, parenting, transmission of AIDS, stress and coping strategies, selfidentity and self-esteem, health beliefs and practices and methods to reach, identify, and predict at-risk individuals). Behavioral pharmacology studies include animal and human laboratory studies on gender differences in the behavioral response to abused drugs in all phases of drug abuse (acquisition, maintenance, withdrawal, and relapse), as well as research focused on menstrual cycle effects on abused drugs and their effects.

• Women and the Health Care System
Numerous studies have established that
women and men interact differently with
the health care system. For example,
women are likely to seek care sooner than
men, and physicians are more likely to
prescribe psychotropic medications for
women. Researchers will study whether
women are therefore at higher risk than
men for the misuse of prescription drugs.
Studies are also needed to show why there
are relatively few women in drug abuse
treatment settings.

### Exchanging Sex for Drugs or Money To Buy Drugs

Drug-abusing women are more likely than drug-abusing men to engage in prostitution, either for drugs or for money to buy drugs. This behavior puts women at high risk for infections, violence, psychological problems, and incarceration. Research will be conducted to study the effects of prostitution on drug abuse, as well as the biological, behavioral, and social needs of prostitutes in drug treatment. Clinicians who work with female drug addicts have

long recognized the connection between prostitution and addiction, although either condition is equally likely to precede the other. However, there is an urgent need for an intensive ethnographic study of the newer phenomenon of frequent sex with many partners for payment of drugs, usually crack cocaine. Also, to develop effective programs to reduce adolescent drug use, scientists need to understand survival sex and its role in drug abuse and other deviant behaviors in street youth, both male and female

### Treating Female Drug Abusers During Pregnancy and Parenting and Independent of Those Roles

Drug abuse treatment for women, until recently, focused primarily on child-bearing and maternal roles. More research, however, is needed on the treatment needs of women regardless of their reproductive status. In addition, research is needed on the special problems and opportunities that can be created by the child care responsibilities of many female addicts. For example, studies are needed to address how day care, housing support, transportation, and parenting skills training can support and enhance drug treatment. New studies will also explore how treatment programs can use the motivation to change, which is often associated with pregnancy and motherhood, to improve treatment outcomes. Previous research has shown that smoking-cessation groups and methadone maintenance can be especially appealing to and effective for women during pregnancy Additional research is needed to show how these gains can be maintained after delivery. Similarly, studies need to be designed to show how to tailor interventions for cocaine abuse to meet the needs of pregnant addicts

### Spread of Tuberculosis (TB) Among Drug Users

In response to the upsurge in tuberculosis and the development of multi-drug-resistant TB strains, a NIDA Program Announcement for research on TB among drug-using populations was published in January 1993. Areas of research interest in this PA include the epidemiology of TB among drug users, clinical issues related to co-infection with HIV, issues of detection of TB infection and

disease, treatment compliance, and related behavioral issues. Gender-specific studies in all these research areas are emphasized

# Treatment for Pregnant Drug Abusers with TB, HIV, or Other Infections NIDA is also greatly concerned about the effects of pregnancy on the treatment of infections and other medical consequences of drug abuse. Although pregnant women are now included in HIV-treatment trials, pregnant drug users still may not be receiving optimal care for their HIV infection or TB. Research is needed to clarify the combined effects of pregnancy and addiction on the course of the disease in women.

### The Effects of Maternal Lifestyles on Infant Outcomes

A recently underway, multisite study is attempting to address a number of methodological challenges facing research on sequelae of prenatal drug exposure This project is a collaboration involving NIDA, the National Institute of Child Health and Human Development and its Neonatal Research Network, the Center for Substance Abuse Treatment, and the Administration on Children, Youth, and Families. The four sites for the study are located in Detroit, Memphis, Miami, and Providence Sixteen thousand infants will be studied in the newborn phase of the project, and 4,000 infants will be enrolled in the follow-up portion of the study. The challenge of detecting possibly subtle developmental effects is being confronted by the use of an assessment battery that measures a wide range of developmental domains using established and more innovative approaches. State-of-the-science medical outcomes are being investigated. Extensive assessment of postnatal environmental factors (e.g., patterns of caretaking and living arrangements) is being carried out. Current plans call for follow-up to 3 years of age, but the agencies involved hope to extend the study beyond that age-This is the largest and most comprehensive study of children born to women who used cocaine and/or opiates during pregnancy It will provide critical new information on drug exposure, environmental conditions, and development. It will also contribute

research methods that should enhance future studies of drug-exposed children.

### Female-Specific Behavioral Treatment Development

Potential adverse consequences of maternal drug abuse for offspring include retarded fetal growth, premature delivery, low birth weight, drug-specific neonatal withdrawal syndromes, poor motor control, and learning difficulties. Previous research has shown that reducing the maternal use of illicit drugs by enrolling and retaining pregnant and postpartum women in drug abuse treatment decreases the harmful consequences for both mother and child.

In addition, drug dependence in women often is accompanied by behavior patterns, such as the exchange of sex for drugs, that subject them to exploitation and violence and increased risk for HIV and other infections. To improve treatment retention and outcomes, research is needed to develop behavioral therapies and psychosocial interventions targeted at women of childbearing age. Research is also needed to assess the impact of adjunct services, such as assertiveness training, counseling to build self-esteem, treatment for psychopathology, and familyplanning and birth-control counseling, on the effectiveness of drug abuse treatment.

Improved gender-specific drug abuse treatment services must also be developed to address the needs of pregnant and postpartum women before, during, and after delivery. Research is needed in three areas: (1) on service delivery factors that affect access to and utilization of treatment and other health services: (2) on drug abuse treatment and social services to pregnant and postpartum women and their offspring, to better understand the extent to which such services can be effectively used to mitigate the adverse consequences of drug abuse and dependence; and (3) on the identification of effective strategies for financing, organizing, and delivering comprehensive, integrated treatment to these populations. Use of financing models such as Medicaid, in concert with other systems such as child welfare services and job training, will be encouraged.

# • HIV-Related Therapeutics in Drug Users (co-issued by NIDA and NIAID)

The purpose of this announcement is to promote research that addresses HIV-related treatment issues among representative samples of drug users to achieve improved clinical management of infected drug users. Research is sought on behavioral, clinical, and pharmacological aspects of treatment medications specific to drug users, including drug interactions, therapeutic efficacy and effectiveness, and psychosocial and behavioral parameters associated with success or failure of a therapeutic protocol. One of the specific areas of research specified in the announcement is gender differences and cultural characteristics in drug-using populations that influence acceptance of available HIV therapeutics and protocol recruitment, retention, and adherence, as well as studies of special drug-using subgroups (e.g., women, adolescents, members of minority groups) that examine access barriers to delivery of HIV-related therapeutics.

# • Strategies To Reduce HIV Sexual Risk Practices in Drug Users

The purpose of this announcement is to introduce a major research effort to develop and evaluate the efficacy of multiphase behavioral change interventions designed to reduce high-risk sexual practices among injecting drug users and/or crack smokers. The announcement notes that many previous HIV-prevention studies have relied on behavioral change models that focus on the individual to change high-risk behavior or use generalized approaches to behavior that are not specific to sexual practices, gender differences, or cultural differences that influence the social context of risk-taking. Thus, the present announcement specifies that interventions must take into account gender, race/ethnicity, sexual orientation, and/or risk behaviors and the social context in which the individual behaviors occurs.

### Conference

NIDA's conference, "Drug Addiction Research and the Health of Women," held September 12 to 14, 1994, indicated that, "despite some promising findings, the basic take-home message is there are more gaps in knowledge

about women in all areas of drug abuse research than there are findings." NIDA plans to start filling those gaps by incorporating into its agenda the conference participants' recommendations that the Institute support more research on the impact of women's biology, environment, relationships, and experiences on health behaviors. Among the areas to be addressed are the following.

- the nature and extent of drug abuse in women;
- women's anxiety and affective disorders that may result in overprescription and abuse of psychotherapeutic agents;
- biological and behavioral mechanisms that may underlie women's patterns of drug use and differences in how drugs affect men and women.
- gender-specific medical and psychiatric consequences of drug abuse, and
- drug abuse prevention and treatment interventions for girls and women

### OFFICE OF AIDS RESEARCH

Since 1993, AIDS has become the fourth leading cause of death for women aged 25 to 44 in the United States, according to recent statistics from the Centers for Disease Control and Prevention (CDC). In 1994, there were 14,081 reported cases of women with AIDS. and CDC estimates that this number represents only a fourth of actual cases. The number of women known to be HIV-infected is steadily increasing. Epidemiologists believe that the actual number of HIV-infected women is greater because many more women either do not yet demonstrate symptoms of infection or are unaware of their infection status. While same-sex contact and needle-sharing once accounted for nearly all HIV infections, now there is an ominous increase in heterosexual transmission. The number of women acquiring HIV through heterosexual contact with infected men has increased dramatically in the United States and now totals more than 36 percent of all cases of women with AIDS

Although black and Hispanic women constitute 21 percent of all U.S. women, they account for more than 77 percent of AIDS cases reported among women in 1994. The

majority of these women live in impoverished communities where injection drug use is prevalent and where access to health care is often inadequate. Of the 5,353 women reported with AIDS in 1994 whose HIV infections were attributed to heterosexual contact, 38 percent reported sexual contact with an IDU and 53 percent with a partner whose risk was not identified. An estimated 80,000 heterosexual women of childbearing age are HIV infected, of whom approximately 7,000 become pregnant every year.

Data suggest that women, particularly young women, may be more susceptible to HIV infection than men, and once infected, women experience gender-specific opportunistic infections and malignancies (e.g., vaginal candidiasis, genital papillomavirus infections, pelvic inflammatory disease, abnormalities of the cervical tissues, and a greatly increased incidence of precancerous cervical and vaginal lesions). As the pandemic claims more women's lives, NHI has moved to address the multi-Jaceted biological and behavioral issues related to HIV infection and women. NIH has developed a multifaceted approach to gaining insight and understanding of the complex scientific, sociological, and psychological nature of HIV disease in women. In addition, a high priority has been placed on research to improve the diagnosis, treatment, prevention, and control of HIV infection and its sequelae in women. The majority of the institutes, centers, and divisions of NIH are actively involved in supporting these efforts

The increasing numbers of HIV-infected women in the United States, however, reflect to a lesser degree the numbers of women around the world who are infected or affected by HIV infection and AIDS. The World Health Organization (WHO) estimates that 7 to 8 million women of childbearing age worldwide have become infected with HIV, including 5.5 million in Africa and 1.3 million in south and Southeast Asia According to the WHO, adolescent girls and young women represent a majority of the new cases among young people aged 15 to 24 who become HIV infected worldwide, and this age group represents 50 to 60 percent of new HIV infections. Estimates are that more than 13 million women will have become infected with HIV by the year 2000, and about 4 million of them will have died

### Accomplishments

### **Transmission**

Natural history and epidemiology studies have demonstrated the changing demographics of HIV infection and AIDS from an illness primarily afflicting homosexual and bisexual men to the current pandemic afflicting women. children, adolescents, minority populations. and injecting drug users. Natural history and epidemiology studies continue to provide crucial information concerning heterosexual transmission of HIV and transmission of HIV from infected mothers to their children, as well as HIV transmission that is related to needle-sharing and drug abuse. In addition. these studies provide important baseline data that can be used in determining the efficacy of potential therapies and vaccines for the treatment of HIV and its sequelae.

# The Women's Interagency HIV Study (WIHS)

Primarily sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and the Agency for Health Care Policy and Research, WIHS is a collaborative, multisite, longitudinal study designed to investigate the impact of HIV infection on women in the United States. The study population, once enrollment is complete, will include approximately 2,000 HIV-infected women and 500 HIV-uninfected women at high risk of acquiring HIV who are age 13 years or older. This study is designed to (1) determine the spectrum and course of clinical manifestations of HIV infection in women, (2) identify the pattern of immune markers in HIV-infected women, (3) investigate factors that may delay or accelerate HIVinduced immune dysfunction and specific HIV-related conditions, and (4) study the length of survival and quality of life of women living with HIV infection.

# The Women and Infants Transmission Study (WITS)

Sponsored by NIAID, the National Institute of Child Health and Human Development (NICHD), and the National Institute on Drug Abuse (NIDA), the study is a collaborative, multicenter study that includes the natural history of HIV infection in infants infected in utero and women who have recently delivered babies. WITS II is recruiting only HIV-infected pregnant women and their offspring and follows all postpartum women and their

children from WITS. WITS II also examines factors related to HIV progression in women during pregnancy.

# The Mother-Infant Transmission Cohort Study (MITS)

Co-sponsored by NICHD and the National Cancer Institute (NCI), the MITS study is a multicenter natural history study of the vertical transmission of HIV from mother to child. The identification in this study of a potential protective role for maternal anti-gp120 antibody may be a significant factor in the development of a vaccine to prevent maternal-fetal transmission.

### The International HIV Twins Registry

This is an NCI-initiated resource that is used to identify characteristics of HIV infection in twins. An analysis of the registry has shown greater risk for transmission in the firstborn, which suggests that vaginal exposure to the virus in the birth process may play a significant role in transmission of HIV to the newborn. An additional analysis of the twin registry data suggests that approximately 60 percent of the mother-to-infant transmissions occur at the time of birth. Based on this data, NCI and NIAID scientists designed a clinical trial of inexpensive, readily available, viricidal solution to cleanse the birth canal in an effort to lower risk of HIV infection in this setting.

### Natural History Studies

- NICHD and the Fogarty International Center studies are examining the possible benefits of vitamin A supplementation in reducing mother-to-child transmission.
- NIAID and the Fogarty International Center studies are examining the possible benefits of community-based mass administration of sexually transmitted disease prophylaxis in preventing heterosexual HIV transmission.
- NCI has established the Multi-State AIDS/ Cancer Match Registry linking AIDS and cancer registries in five areas of NCI's Surveillance, Epidemiology and End Results (SEER) program (San Francisco, Los Angeles, Atlanta, Detroit, and Connecticut) and 10 other sites (New York City and State, New Jersey, Puerto Rico, San Diego, Sacramento, Florida, Illinois, Colorado, and Massachusetts). This database allows for the first time quanti-

tative estimates of rare as well as common malignancies.

- The NCI-sponsored Gynecology Oncology Group is conducting a pilot clinical trial to evaluate the toxicity and antitumor efficacy of combined retinoid+interferon-alpha with and without azidothymidine (AZT) for anal or cervical dysplasia and cancers occurring in HIV-infected individuals
- The NIAID-sponsored Preparation for AIDS Vaccine Evaluation program studies various aspects of HIV infection and its sequelae in cohorts of at-risk women and men in eight countries.
- NIAID is examining prevention techniques directed at reducing mother-infant transmission through its HIV Vaccine Efficacy Trials Network (HIVNET) international sites. Prevention efforts under consideration include trials to reduce infection of the baby through vaginal and newborn cleansing, treatment of prenatal STDs, and evaluation of micronutrients
- An ongoing series of NIDA-supported longitudinal studies are investigating biological and behavioral aspects of the natural history of HIV in female drug users. Both seroprevalent and seroincident cohorts of former and active drug users are being prospectively followed.
- The National Institute of Nursing Research studies examine the effect of gender differences in the adaptation of young people to HIV infection, the influence of psychosocial variables in influencing high-risk behavior, and the impact of psychoeducational intervention.
- The National Heart, Lung, and Blood Institute supports research on the cardiac complications of HIV infection in women that is studying whether the natural history of HIV-related cardiac disease differs in women.
- The National Institute of Dental Research (NIDR) study—titled "Oral Manifestations of the Acquired Immunodeficiency Syndrome" (AWARE)—is examining the oral manifestations of HIV infection. In addition, the NIDR Partner's Study is examining heterosexual transmission of

- HIV. NIDR also sponsors studies on the oral manifestations of HIV in different risk populations and the identification of HIV inhibitory salivary factors
- NCI scientists continue to define the immunoepidemiology of transmission of HIV infection from mothers to newborns Both humoral and cellular mechanisms impede the transfer of HIV infection from mother to fetus in utero and/or delay the onset of active HIV infection in infants
- The National Institute on Deafness and Other Communication Disorders sponsored a study on the role of AIDS-associated immunosuppression on the rate and severity of congenital cytomegalovirus (CMV) infection. Fetal CMV infection is becoming a public health problem in the population at large, with postnatal consequences ranging from severe generalized illness to more subtle neurological defects, including deafness and other communication disorders.

Studies on AIDS-Related Cervical Cancer Cervical dysplasia is seen frequently in HIV-infected women. While this may be due partly to the increased number of sexual risk factors associated with this population, the immunosuppression resulting from HIV disease exacerbates the course of infection with the human papilloma virus, the strongest epidemiologic risk factor for cervical dysplasia Further evidence of a causal association between HIV infection and cervical disease is the increased severity of this condition in infected women and its relative resistance to treatment.

### Planned Activities

Future natural history studies sponsored by the National Institutes of Health will do the following:

- determine the factors related to transmission and disease progression in affected populations, with special emphasis on women, children, adolescents, minorities, and injecting drug users;
- examine factors that influence the infectivity of individuals in various stages of the disease, such as HIV shedding in semen;

- determine the role of sexually transmitted diseases and genital lesions in HIV transmission and disease progression;
- ascertain the effects of antiviral therapies on transmission;
- evaluate the effects of oral and barrier methods of contraception on the acquisition of sexually transmitted diseases and on HIV transmission;
- identify specific markers of disease activity and the effects of therapy on these markers;
- define specific risk factors associated with the development of various disease complications; and
- further define the spectrum of diseases affecting HIV-infected women.

### Treatment

The discovery and development of new agents for the treatment of HIV disease, including its associated opportunistic infections, are critical efforts in the NIH's AIDS research program. NIH supports two major approaches to drug development: drug screening and targeted drug development programs. The screening approach involves the testing of natural and synthetic compounds for anti-HIV activity. Targeted drug development involves characterization and delineation of the structural biology of HIV for the purpose of developing agents targeted at inhibiting specific steps in the HIV life cycle.

NIH has placed a high priority on the evaluation of therapeutic regimens for the treatment and control of HIV infection and its sequelae in women. Three institutes of NIH have the primary responsibility for the clinical trials programs: NIAID, NICHD, and NCI.

NIAID program includes a nationwide AIDS clinical trials network, the AIDS Clinical Trials Group (ACTG), which consists of 57 units (ACTUs) located at major medical centers. In addition, NIAID sponsors the Terry Beirn Community Programs for Clinical Research on AIDS, which involve 16 sites; the AIDS and HIV-Related Research Intramural program; and the Division of AIDS Treatment Research Initiative, which has more than 50 sites.

NICHD has established 28 centers nationwide to test potential therapeutic agents

in HIV-infected women, children, and adolescents. With the consolidation of the NICHD and NIAID clinical trials units to form the Pediatric ACTG, this clinical trials system conducts and supports therapeutic research in HIV-infected pregnant women and children.

NCI has developed an adult and a pediatrics AIDS Intramural Unit located at the NIH Warren Grant Magnuson Clinical Center that has conducted pioneering studies of several novel anti-HIV agents and new antimycobacterial agents.

The National Center for Research Resources (NCRR) provides the infrastructure for many of the ACTUs through either its General Clinical Research Centers (GCRCs) or the Research Centers in Minority Institutions (RCMI) programs. The GCRCs are uniquely positioned to collaborate and contribute to AIDS clinical trial research, with 52 of the 75 GCRCs involved in this research effort. The RCMI program provides infrastructure support for clinical trials research at several institutions with large numbers of underrepresented individuals.

### Clinical Trials

The NIH sponsors intramural and extramural clinical trials of potential therapeutic agents in single or multidrug regimens to determine drug safety and efficacy in the control and treatment of HIV infection and its accompanying opportunistic infections and malignancies. Clinical trials accomplishments and ongoing activities include the following:

An NIAID/NICHD-sponsored, phase III clinical trial (ACTG 076) determined that AZT given to HIV-infected pregnant women antepartum and intrapartum, as well as to the newborn during the first 6 weeks of life, reduced the risk of maternal-infant transmission of HIV by two-thirds.

An interim analysis of the ACTG 076 study demonstrated a significant reduction of the risk for transmission of HIV from mother to infant for the group who received AZT. The study was conducted by the NIAID Pediatric ACTG in collaboration with NICHD, the Institute National de la Sante et de la Recherche Medicale (INSERM), and Agence Nationale de Recherches sur le SIDA (ANRS) in France. The study involved 35 NIAID-sponsored sites, 15 NICHD-sponsored sites, and 9 centers in France.

An independent Data Safety Monitoring Board recommended that women who have not yet delivered and infants who are less than 6 weeks old in the study should immediately be offered AZT. The board emphasized the importance of long-term follow-up of infants enrolled in the study to monitor for the possible development of unknown late effects of study treatment

In early 1995, the Public Health Service will develop Recommendations for HIV Counseling and Testing of Pregnant Women. These recommendations will provide a framework for health care providers to (1) enable HIV-infected pregnant women to know their infection status, (2) advise infected women of ways to prevent perinatal, sexual, and other transmission of HIV, (3) facilitate appropriate follow-up for HIV infected women and their infants, and (4) assist uninfected pregnant women in reducing their risk of infection

- NIH is continuing to support efforts to enroll women in all clinical trials programs
- NCI and NIAID jointly develop AIDSrelated clinical trials of potential agents targeting malignancies unique to women
- NIAID and NIDA are collaborating to increase participation of HIV-infected female and male injecting drug users in ACTG clinical trials
- A clinical protocol has been implemented to evaluate hyperimmune anti-HIV immunoglobulin for the prevention of maternal-fetal transmission of HIV.

Ongoing NIH-sponsored clinical trials related to women and AIDS include (1) a gender-specific opportunistic infections protocol studying the efficacy of fluconazole prophylaxis for mucosal *Candida* infections in HIV-infected women, (2) an evaluation of the safety of AZT during the third trimester of pregnancy, and (3) a study of the safety of recombinant CD4-Immunoglobulin *G* in the last trimester of pregnancy.

### Animal Models

NIH-sponsored drug discovery and development programs in the area of women and HIV include an NIAID contract awarded as part of a

program initiative concerned with the Evaluation of Pharmacokinetics of AIDS Therapies in Non-Human Primates Studies are being conducted in pregnant or infant macaques and in other primate models of pediatric AIDS to test the efficacy and pharmacokinetics of potential AIDS therapies, which will be instrumental in the design of clinical trials in HIV-infected pregnant women or children. In addition, the National Institute of Environmental Health Sciences (NIEHS) supports studies investigating the toxic effects of HIV therapies using rodent models of both sexes NIEHS studies ascertain the effects of potential therapeutic agents and their combinations on pregnant rodents and their developing fetuses as a model applicable to pregnant women. As new drug combinations are developed for HIV infection and AIDS. NIEHS-sponsored reproductive and toxicity studies will be invaluable in assessing gender-specific and gender-neutral effects of these combinations, as well as in assessing the potential effects of proposed therapies for preventing maternal/fetal transmission of HIV

Vaccine Development

The development and evaluation of a safe and elfective AIDS vaccine(s) is an international public health priority and a major goal of NIHsponsored research. Various strategies to stimulate a protective immune response against HIV infection are being explored, and efforts are being made to determine which of these strategies offer the most promise for further development. In addition, potential vaccines are being explored as agents that may prevent transmission from mother to fetus as well as serve as immunomodulators to improve immune function and diminish disease progression in individuals who are already HIV-infected Several approaches currently being pursued in the development of vaccines include the use of synthetic viral peptides, recombinant products, and genetic recombinant products The HIV Vaccine Working Group has been established to coordinate NIAID vaccine efforts. Members include NIH intramural and extramural scientists, NIHsponsored scientists, and representatives from community constituency groups.

The NIAID-sponsored National Cooperative Vaccine Development Groups, which consist of six awardees, have been established for the discovery and development of vaccine candidates. Research teams composed of scientists from

industry, academia, and government collaborate to develop and test novel experimental HIV vaccine concepts using the SIV model.

NIAID sponsors a number of other HIV vaccine-related activities:

- A program titled Collaborative Mucosal Immunology Group for AIDS Vaccines was designed to develop vaccine strategies and basic research on primate mucosal immunity to protect against transmission of HIV.
- A program titled "Correlates of Immune Protection in AIDS Vaccine Recipients" seeks to define the correlates of immune protection against HIV through the intensive immunology, virology, and molecular biology studies. These studies compare (1) vaccine trial participants who become infected with HIV to those vaccinees who remain uninfected despite high-risk behavior, (2) long-term nonprogressors to infected individuals who have a rapid disease course, and (3) individuals who appear to escape infection despite repeated exposure to the virus with those who quickly become infected after similar exposure. Such studies may elucidate genetic or biologic factors that affect the body's response to HIV exposure and infection.
- NIAID's variation project was established to investigate the rate and magnitude of genetic and immunologic variation of HIV and related retroviruses, determine the biologic consequences of HIV variation, and explore the impact of HIV variation on strategies for vaccine development. Such studies are important because production of an HIV vaccine is made much more difficult by the high frequency with which HIV mutates as well as by the differences in the regional distribution of certain subtypes of HIV. HIV mutations can result in subtle but significant changes in viral structure that could render a potential vaccine ineffective.
- NCI-sponsored investigators are attempting to develop vaccine candidates for human papilloma virus associated with cervical dysplasia and cancer. Human papilloma virus, like other viruses, possesses proteins capable of eliciting immune responses.

### Vaccine Clinical Trials

The AIDS Vaccine Evaluation Group has established six AIDS Vaccine Evaluation Units designed to evaluate potential vaccines in phase I and II trials. Women make up 50 percent of the participants in these trials. Significant progress has been made in the development of potential vaccines for the prevention of HIV infection. For example, all vaccine candidates tested to date in phase I trials have been shown to be safe and well tolerated. Phase I trials involving HIV seronegative individuals have shown that the majority of vaccine candidates produce binding antibodies. Titers of neutralizing antibody directed toward homologous virus, however, were low. The vaccines in these trials also produced low or nonexistent neutralization titers against heterologous virus, and the duration of the response lasted only from weeks to months. More positive results have been observed in recent studies testing a recombinant vaccinia virus gp 160 vaccine candidate followed by a booster of a recombinant subunit vaccine candidate. This regimen produced functional CTLs capable of destroying HIV-infected cells.

NIH has initiated phase II trials of two gp120 vaccine candidates in uninfected atrisk individuals. Also, NIH will soon initiate the first phase II trial of a vaccine candidate in HIV-infected individuals to prevent or delay disease progression and/or to inhibit viral load. A trial in HIV-infected pregnant women will study the possibility of preventing maternal-fetal transmission with a vaccine. In order to characterize the types of responses illicited by different vaccine candidates, NIAID will evaluate serum samples from these study participants using sophisticated techniques.

To prepare for the possibility that these or other candidates may show promise for large-scale phase III testing, NIAID developed the HIVNET, a network of clinical sites to conduct HIV vaccine efficacy trials in at-risk populations, both in the United States and abroad. NIAID is proceeding with its efforts to establish the necessary infrastructure at these sites.

### Rhesus Macaque Model

Major developments have resulted from studies using the SIV model in the Regional Primate Research Centers Program supported by NCRR. NIH-sponsored investigators at the NIAID-funded SIV Vaccine Evaluation Units have demonstrated that molecularly cloned SIV can induce disease in rhesus monkeys remarkably similar to AIDS in humans. In addition, studies have shown that a whole, inactivated SIV vaccine, a live attenuated vaccine, a live, recombinant vaccinia vaccine, and a component SIV vaccine composed of viral protein surface molecules are each effective in preventing SIV infection in other macaques. Planned NIH activities will further integrate the SIV/rhesus macaque model into vaccine development and evaluation programs

Female-Controlled Prevention Approaches Several NIH institutes, centers, and divisions sponsor biomedical research focused on blocking heterosexual transmission of HIV with chemical and physical barriers. NIAID and NICHD are the major sponsors of research in this area.

NIAID is establishing a mechanism to identify and develop potential virucidal agents that might be topically administered by women to prevent sexual transmission of HIV. Factors being considered include maintenance of normal vaginal pH and microbial content, ease of use, long-lasting effect, and the possible adverse effect on sperm activity and on normal hormonal activity. Once an agent with appropriate pharmaceutical properties is developed, testing will be done in animal models to determine efficacy and safety.

Topical microbicides are products, such as gels, foams, creams, and films, that prevent sexually transmitted infections. These products are designed for intravaginal/rectal use and may or may not be spermicidal (i.e., contraceptive). In 1993, NIAID launched an extensive program entitled the "Topical Microbicides Research Initiative," which consists of three parallel tracks: basic research, product development, and clinical evaluation, including behavioral research on acceptance and compliance. To further basic research required for the development of new products, NIAID has funded three Topical Microbicides Program projects. In addition, NIAID has contracts for in vitro and in vivo screening of antiviral/ antimicrobial compounds. Currently, NIAID is funding a phase III clinical trial measuring the efficacy of nonoxynol-9 (N-9) containing spermicidal film. Studies are currently underway to evaluate the efficacy of formulations to prevent transmission of HIV in different

cell lines; additional safety studies of other N-9 spermicidal products are planned.

NICHD funds directed research on the medical effects of oral contraceptives, intrauterine devices, condoms, spermicides, and other contraceptive drugs and devices available in the United States. As part of its research portfolio, NICHD evaluates the role of barrier contraceptives in preventing sexually transmitted diseases and HIV infection and studies the impact of oral contraceptives on disease susceptibility and progression relative to the cervical and vaginal environment and the immune system.

NICHD planned research activities include the following.

- a case-control study of reversible contraceptives and incident HIV infection;
- a clinical trial of spermicides for prevention of HIV infection;
- a study of the side effects of vaginal inserts that might increase susceptibility to HIV infection.
- studies on nonlatex condom efficacy; and
- a group of studies on unintended pregnancy in the United States, including the dynamics of contraceptive behaviors.

The Fogarty International Center also sponsors several programs investigating the use of barrier methods for prevention of HIV transmission to women from HIV-infected males. Some of these studies are conducted in parts of South America and Africa.

### Hormonal Contraceptives

Studies on steroid contraceptives are of particular importance for the potential impact on HIV-infected women and those at high risk of infection. NICHD is conducting a number of studies to address critical issues related to the impact of steroid contraceptives on HIV-infected women and those at risk of infection including:

- studies on whether contraceptive steroids might alter susceptibility to HIV and other diseases;
- study to determine whether progestintreated monkeys are at increased risk of infection when vaginally exposed to HIV; and

 studies on possible mechanisms by which contraceptive use might affect the progression of disease in women already infected with HIV.

### Barrier Contraceptives

NICHD also supports research to evaluate barrier methods of preventing HIV infection. NICHD has completed a major laboratory program at UCLA to evaluate the suitability of using condoms and condoms plus spermicides in preventing HIV transmission. The results indicated that condoms available in the United States are of high quality and should provide a substantial degree of protection from HIV infection and other sexually transmitted diseases (STDs). Additional studies supported the findings that spermicides plus condoms might offer additional protection against HIV infection. The possibility that spermicides decrease the risk of STDs is derived from both in vitro and in vivo studies. As part of the NICHD project described above, laboratory experiments also were conducted on six spermicides to determine their inhibitory concentrations against nine STDs and HIV. The findings showed that all spermicides tested inactivated HIV. Although all available spermicides inactivate cell-free HIV in vitro and clinical trials have documented the efficacy of these agents for the prevention of some STDs, the efficacy of spermicides for the prevention of HIV infection in actual practice needs to be documented.

Epidemiologic studies will offer the most direct evidence for a protective effect of barrier contraceptives for the prevention of HIV infection. NICHD is therefore conducting a prospective observational study to determine the degree to which male latex condoms and spermicides reduce the incidence of gonorrhea and chlamydia in women at high risk for STDs. Early in 1995, the female condom will be introduced to this study as an additional intervention. The augmented study will measure the protection afforded by each method compared to those who do not use barriers and will include enough users of both the female condom and the male condom so that these methods can be compared to each other for efficacy. Although this study would ideally include evaluation for the prevention of HIV infection, the low incidence of HIV disease in any population available for the study in the United States makes the inclusion of this outcome impossible

at this time. Adequate quantitation of the protection against more common diseases will provide indirect evidence of protection against HIV, since HIV is transmitted through genital lesions and through exchange of blood and semen.

NICHD has developed a statistical model to project the effect of condoms on the AIDS epidemic in the United States. The results from this model provide assurance that condoms can be recommended as protection from HIV infection for those at low risk, even in the absence of quantitative data about condom efficacy. However, for those individuals at high risk of HIV infection (e.g., those with partners known to be infected), the uncertainty about the exact efficacy of condoms makes their use problematic.

NICHD also sponsors research focused on the development of a disposable diaphragm. The objective of this project is to develop a spermicide-releasing, disposable diaphragm with increased potential for high efficacy and acceptability. The development of this product may allow women to protect themselves against the transmission of HIV, particularly in situations where male condom use is not culturally acceptable.

### Prevention and Intervention

The study of AIDS has presented significant challenges to both the biomedical and social and behavioral science research communities. Prevention of HIV infection involves behavioral changes in areas of life where such change may be difficult to effect.

An important component of NIAID's vaccine research agenda involves selected prevention research. This includes research examining the effectiveness of virucides, STD treatments, and other strategies (e.g., vaginal washing) in preventing transmission of HIV. NIAID has initiated studies of (1) HIV prevalence and risk factors among youth aged 18 to 21 years living in an inner-city neighborhood in New York City where HIV prevalence among injection drug users is high; (2) widespread administration of anti-STD chemotherapy on HIV incidence in rural Uganda; and (3) nonoxynol-9 as a topical virucide in a controlled clinical trial among at-risk women.

Despite the overwhelming risks presented to them, women have the fewest available means for protection against HIV and other STDs. A considerable obstacle in preventing heterosexual transmission is the absence of an inexpensive, reliable method that women can use to protect themselves without their partner's consent. Chemical methods that can be distributed quickly and inexpensively and are controlled by women might have a powerful impact on the spread of HIV infection.

### Behavior/Prevention

NCI scientists, in conjunction with scientists from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute of Mental Health (NIMH), continue to dissect genetic factors that may potentially contribute to complex human characteristics and diseases in both males and lemales. Attributes under study include sexual orientation, susceptibility to alcoholism and substance abuse, and interindividual variations in immunopathogenetic response to HIV infection and progression to AIDS.

NICHD research program in behavior/ prevention builds on research examining the choices individuals make regarding their sexual behavior and protection against adverse outcomes of those behaviors, such as unwanted pregnancy or STDs NICHD research focuses on conceptualizations of disease, particularly diseases that are unlikely to be known to the individual through direct experience. The intervention research builds on previous family planning studies as well as proven interventions for smoking and other healthrelated behaviors.

NICHD has undertaken a major program of research in an effort to understand the effect of HIV/AIDS and STDs on choices regarding sexual and reproductive behavior. This research makes use of a wide range of populations, including national probability samples, regional samples of minority adolescents, clients of high school health clinics, teens in detention centers, clients of STD clinics, and male prostitutes. These studies use the Health Belief Model, the Subjective Expected Utility Model, and other theoretical constructs to examine questions relating to how the risk for HIV infection and AIDS affects behavior. These studies are producing data that elucidate patterns of sexual behavior and protective behavior and their relationships to a variety of social and background variables.

Specifically, NICHD sponsors research on reducing the risk of sexually transmitted HIV

infection, preventing HIV-infection in sexually active adolescents, teaching youth social skills, evaluating AIDS prevention efforts, assessing social context for adolescent high-risk sexual behavior, understanding decisionmaking processes in youths regarding AIDS risk behavior, and understanding the development of attitudes and knowledge about AIDS.

NIMH prevention programs provide support and funding for the following studies.

- The Multisite HIV Prevention trial is a phase II/phase III study to test the efficacy of an HIV prevention program in seven sites with multicultural populations that include African-American and Hispanic women. The trial is the only controlled multisite, multiple population prevention study being conducted. In contrast to individual intervention research projects that yield single-site outcome data of limited generalizability, the trial is designed to be a model for conduct of prevention activities in public health settings as well as in HIV vaccine trials. The multisite trial constitutes a major commitment of research expertise to the challenge of understanding the efficacy of HIV riskreduction interventions tailored to the disenfranchised populations most vulnerable to the next wave of the HIV epidemic The goals of this multisite trial are to provide an intervention to meet two critical public health needs: quality HIV prevention service delivery and behavioral interventions for vaccine trials.
  - Studies of preventive intervention programs, several of which target inner-city women, are being conducted. A study conducted with women in family planning clinics has been successful in reducing high-risk behavior. Another of the ongoing studies is evaluating intensified case management as an effective intervention to reduce risk behavior of cocaine-addicted pregnant women.
- A study of inner-city African-American adolescent girls who are sexually active and at high risk for HIV infection is evaluating whether increasing skills at negotiating difficult sexual situations and enhancing ability and motivation to implement safer sexual practices are more effective than knowledge-only interventions.

In addition, NIDA supports a research program to develop a variety of effective, cost-efficient comprehensive programs. These programs offer a continuum of care designed to reduce the use of illicit drugs and related high-risk behaviors and thereby reduce the risk of HIV infection among drug-abusing women. Research initiatives scheduled for implementation include clinical studies focused on psychotherapy, behavior therapy, and other psychosocial interventions: treatment evaluations to assess strategies to improve entry and retention in treatment and improve compliance with treatment regimens; and health services studies to understand the impact of organization, structure, financing, management, and staffing patterns on the availability, accessibility, and utilization of therapeutic and preventive interventions.

NIAAA is sponsoring research on alcohol use/abuse and unsafe sexual practices with the goal of understanding the salient decisionmaking processes and of developing social-psychological prevention and intervention strategies to reduce the risk of female alcohol-related HIV exposure. Studies of HIV-infected women focus on female partners of bisexual males, women alcoholics in treatment programs, and school-based prevention research programs for adolescent girls.

NIAAA also sponsors several studies on the relationship among adolescents between alcohol use and risk for HIV infection as a consequence of engaging in high-risk sexual behaviors and on risk factors for HIV transmission among alcoholics who also participate in needle-sharing activities or drug use.

### AIDS-Related Research Resources

### Training and Infrastructure

NIH supports a number of intramural and extramural research resource programs. Included in these programs are grants for training AIDS researchers, developing animal models, and constructing or improving facilities and equipment for AIDS research. Several of the NIH institutes, centers, and divisions have developed pre- and postdoctoral programs to provide training for scientists from the United States and abroad in AIDS-related research areas such as epidemiology, molecular biology, and immunology.

NIAID supports the Centers for AIDS Research (CFAR) program that consolidates, focuses, and enhances the capacity for basic and applied research on AIDS within leading research institutions by fostering the creation and development of coordinated scientific and administrative functional units. CFAR also supports the administration, planning, and evaluation of multiple AIDS research projects, symposia and seminars on AIDS research, as well as the publication of newsletters to keep scientists and the public apprised of the latest developments in AIDS research and related issues. In addition to salaries, equipment, and supplies, CFAR funds may be requested for alterations and renovations to upgrade laboratories to conduct studies on HIV and related retroviruses.

The Fogarty International Center supports postdoctoral and epidemiology training programs for AIDS-related research to increase the number of skilled scientists, particularly from developing countries, who are able to confront this pandemic. These programs support research in such key areas as HIV infection among women and new preventions and treatments for AIDS-related OIs.

### Information Dissemination

NIH believes that information concerning standards of care, the results of clinical trials with immediate relevancy, options for trials, and eligibility criteria for entry into trials must be disseminated as rapidly as possible. NIH continues to develop information dissemination mechanisms designed to expedite dissemination of the latest findings on state-of-the-art therapies, health care, and prevention techniques to domestic as well as international audiences as appropriate.

The National Library of Medicine (NLM) develops, maintains, and publicizes a variety of AIDS-related information services to support the work of AIDS researchers and practitioners and to assist the public in identifying sources of AIDS-related information written for a general audience. NLM has a comprehensive collection of AIDS-related literature directed toward health professionals and researchers that is described in the AIDSLINE database. In cooperation with NIAID and other PHS agencies, NLM also produces AIDSTRIALS, a database of AIDS-related clinical trials, and AIDSDRUGS, a database of information on experimental therapies listed in AIDSTRIALS that are currently being tested as treatments for HIV-related disorders. As part of its DIRLINE (Directory of Information Resources ONLINE) database, NLM maintains a directory of organizations that are sources of AIDS-related information directed at health professionals, community

leaders, and the general public. About 32 percent of the organizations that dispense AIDS-related information produce materials related to pregnant women and children

In 1993, NLM and the Office of AIDS Research co-sponsored a conference to identify the information needs of all the constituency groups involved in HIV/AIDS! researchers, health care providers, and the affected communities. As a result of recommendations from this conference. NLM has initiated several outreach efforts aimed at improving community access to information. Among these are a series of small awards to community organizations and public libraries that are working to bring HIV/ AIDS information to particular populations. including women and children, as well as specifically targeting at-risk adolescents. An evaluation of the effectiveness of the different approaches being tried will, it is hoped, lead to more effective techniques of ensuring access

To meet the need for timely, accurate information, a Public Health Service Interagency Coordinating Group implemented the HIV/AIDS Freatment Information Service (ATIS) in 1994. ATIS is a toll-free telephone reference service for health care and HIV service providers and for people with AIDS who want to know about federally approved HIV/AIDS treatment options. ATIS is staffed by reference specialists who are health care professionals. To answer questions, ATIS staff use the NLM database of HIV/AIDS treatment guidelines.

The NCI Physician's Data Query (PDQ) is a comprehensive cancer database that provides state-of-the-art information on diverse facets of cancer medicine, including AIDS-related malignancies. PDQ serves as a focal point for information dissemination to both professional/scientific and public/patient audiences regarding cancer prognosis and treatment (including literature citations), supportive care, screening and prevention, investigational drugs, clinical trials protocols, and directories of cancer-care physicians and organizations. PDQ contains current information in each of these areas for AIDS-related cancers in women.

A PHS collaborative project, the AIDS Clinical Trials Information Service is a central resource providing current information on federally and privately sponsored clinical trials for HIV-infected individuals. The AIDS Clinical Trials Information Service features experienced health

specialists who provide information about AIDS clinical trials. These specialists access a database of up-to-date, accurate information on AIDS studies currently underway and answer questions from individuals infected and affected with HIV and their families, as well as from health professionals. They provide information regarding (1) purpose of the study. (2) studies that are open, (3) study locations. (4) eligibility requirements and exclusion criteria, and (5) names and telephone numbers of contact persons.

### Initiatives

Basic research sponsored by NIH has provided and will continue to provide a better understanding of the origins, pathogenesis, and early etiology of HIV infection and HIV-associated opportunistic infections and malignancies in women. NIH also is continuing to support drug and vaccine development efforts designed to identify and develop new regimens targeted toward women as well as behavioral studies related to the development of intervention programs and the use of barrier contraceptive methods

Planned NIII-sponsored natural history studies will continue research on (1) the unique manifestations of HIV infection among women. (2) basic research into biological factors associated with heterosexual HIV transmission, (3) perinatal transmission issues, and (4) research on clinical, immunologic, virologic, endocrine, biologic, behavioral, and psychosocial aspects of HIV infection and its treatment in women in all populations

NIH will continue to place high priority on the evaluation of therapeutic regimens for the prevention, treatment, and control of HIV infection and its sequelae in women and to provide support for ancillary services to enhance the enrollment of women in clinical studies. Special committees within the clinical trials networks will continue to address unique issues associated with women and HIV. These committees specifically will continue to (1) enhance participation of women in clinical trials and review entry criteria to ensure that trials do not exclude women, (2) ensure that clinical trials contain gynecologic recommendations to meet the medical needs of HIVinfected women, and (3) facilitate the design and development of clinical trials testing treatments for HIV-associated conditions that specifically affect women.

# Appendix Office of Research on Women's Health Research Awards

### FY 1993 ORWH RESEARCH SUPPORT

- ► Special Research Initiatives
- ► Administrative Supplements to Ongoing Research Grants

### SUMMARY OF FY 1993 SPECIAL RESEARCH INITIATIVES

### Developmental/Reproductive Biology

► Title: Biology and Pathophysiology of Endometriosis and Leiomyomata

uteri (myoma)

ICD: NICHD

Key Words: endometriosis, leiomyomata uteri

Funds will be provided for a second year to support six grants for research into the biology and pathophysiology of endometriosis and leiomyomata uteri (myoma). Directives from the 102nd U.S. Congress have urged NIH to address research efforts toward several diseases and conditions related to women's health including endometriosis and myoma. Goals for this research for endometriosis are to improve diagnosis and therapy and for myoma are to gain knowledge about initiation and growth and to develop safe, long-term medical therapies. Award Amount: \$800,000.

► Title: Computerization of the Carnegie Collection of Human Embryos

ICD: NICHD

Key Words: embryology, pathology

Currently in its second year, this project is producing high-resolution digital images of both normal and abnormal embryos during all stages of development. The database that will be developed will be available nationwide to increase our understanding of human development and to assist in diagnosis and prevention of birth defects. Award Amount: \$10,000.

### Cancer

► Title: DES Education Materials

ICD: NCI

Key Words: DES exposure, education materials

ORWH provided support for research in response to an RFA. Three grants were awarded by NCI through a cooperative agreement to target DES-exposed mothers and their children for an educational campaign regarding: cancer screening, infertility information, and diagnosis and treatment. The grants are from California, Massachusetts, and New York. The information will also be designed to target physicians for the same type of information. The grants are being co-sponsored by NCI, ORWH, and NICHD. An RFA is going to be reissued to target other parts of the Unites States including the South, Midwest, and Mid-Atlantic. Award Amount: \$50,000.

### Temporomandibular Joint Disorders

Title: Evaluation of the Reliability of Newly Developed Research Diagnostic

Criteria for TMDs

ICD: NIDR

Key Words: diagnostic criteria, TMD

Funding will support the assessment and improvement of the reliability of a newly developed and comprehensive set of diagnostic criteria developed to facilitate research on TMDs through the development of forms, protocols, and calibrated manuals to be used in collecting data on reliability; coordinating data entry and analysis. Award Amount. \$4,500

### Infectious Diseases

► Title: Prevention of Maternal-Fetal Transmission of SIV and HIV

ICD: OAR

Key Words: AIDS, maternal-fetal transmission, viral transfer

A macaque model for maternal-fetal transmission of retroviruses indicates a rate of 33 percent incidence of maternal-fetal transmission, similar to the rate in children born to HIV-I infected mothers. Funding will be directed at using antiviral compounds at various times during pregnancy to determine the optimum time of antiviral treatment. The model will provide data on the time of viral transfer, the effect of maternal antibodies on viral transmission, and the efficacy of antivirals on the prevention of transmission. Award Amount. \$16,500.

► Title: Intervention Trial of Vaginal Cleansing to Reduce

Perinatal Transmission of HIV-I

ICD: OAR

Key Words: maternal-fetal transmission, vaginal cleansing

Data indicate that second-born twins are at two- to fourfold lower risk of HIV-I infection than firstborn twins. This supplement will test the hypothesis that firstborn twins may clean the birth canal and that mother-to-infant transmission may occur as a result of contact with maternal blood or mucus in the birth canal. Clinical trials using Chlorhexidine will be used as a vaginal douche to study efficacy of the intervention and to identify routes of transmission. Award Amount: \$16,500

### Hormonal

► Title: Sex Hormone Regulation of Lacrimal Gland Secretion

ICD: NEI

Key Words: lacrimal gland, dry eye, Sjögren's

The most common manifestation of dry eye is insufficient tear secretion by the lacrimal gland. The condition is associated with women over 45, hormonal causality, and Sjögren's Syndrome. This supplement will provide funds to elucidate some of the molecular mechanisms involved in the regulation of secretion by the female lacrimal gland in female rabbits so that optimal treatment for various causes underlying dry eye can be developed. Award Amount: \$81,500.

► Title: Multiple Roles of Middle Generation Caregiving Women

ICD: NIA

Key Words: caregiving, multiple roles

An increasing number of older women have concurrent responsibilities as caregiver, wife, mother and worker. This panel survey study of 280 middle-aged women seeks to determine the effects of women's caregiving roles on mental, social, and physical well-being. Within women's research related to aging, the controversy over "burdens of women in the middle" versus the positive aspects of "women's multiple roles" is a major unresolved issue. This study is unique in allowing measures over time, attention to somatic and mental health outcomes, and considering several potential outcomes (both positive and negative) of caregiving for women. Award Amount: \$236,654.

► Title: Regional Technology Transfer Meetings

IC: OAR/NIAID

Key Words: technology transfer, AIDS

The sharing of information about advances in AIDS research has proven to be a formidable task, as witnessed by the Annual International AIDS conferences. In 1990 OAR initiated a series of AIDS technology transfer meetings to enhance the sharing of information on treatment and management of symptomatic and asymptomatic patients in coordination with NIAID and HRSA. Capacity meetings were held in San Juan and Mayaguez, Puerto Rico, in FY 1991. OAR will continue this program of targeting areas that do not have a major medical research effort, i.e., Puerto Rico and rural areas of the United States. With respect to dissemination of AIDS technology and AIDS-related research, OAR in collaboration with ORWH plans to expand the program to six meetings in 1993. Award Amount: \$250,000.

### FY 1993 Administrative Supplements to Ongoing Research Grants

### Aging

### Cancer/Behavioral

► Title: Nursing's Impact on Quality of Life Outcomes in Elders NINR
PI: Ruth McCorkle, Ph.D., R.N., University of Pennsylvania, Philadelphia, PA
Key Words: cancer, intervention, quality of life, elderly women

The focus of this supplement will be on older women living alone with a diagnosis of cancer requiring surgery and who have no other identified problems, especially physical and psychological symptoms. Crisis response that accompanies diagnosis, complex physical and psychological symptoms present at hospital discharge, the disproportionate rate of psychological problems among women, and the role that support plays in enhancing coping will be examined. Short-term, standardized, and comprehensive nursing interventions will be designed to enhance quality of life in these patients. Award Amount: \$99,822

### Alzheimer's/Behavioral

Title: Management of Sleep Activity Disruption in Alzheimer's NINR
 PI: Glenna Dowling, Ph.D., R.N., University of California, San Francisco, CA
 Key Words: recruitment, sleep disruption, Alzheimer's, caregivers, Chinese women

Supplemental funds will be used to enhance recruitment of elderly Chinese women and their primary caregivers. The investigators will look at disruption of the sleep-wake cycle and associated illnesses including depression. The nighttime problems of Alzheimer's patients and their caregivers are a major contributing factor in the decision to institutionalize patients. Data will provide scientific information about caregiving behaviors and disease risk. Award Amount: \$49,907

Alcohol, Medications

► Title: Alcohol Use and Drug Interactions in Elderly Women NIAMS

PI: Thomas M. Vogt, M.D., Kaiser Foundation Hospitals, Portland, OR

Key Words: alcohol use, drug interactions, elderly women

Supplemental funds will be used to relate patterns of alcohol and medication use to the functional status, cognition, mood, and social functioning of elderly women. This information will complement the major goal of the parent grant to determine relative risk factors for falls and osteoporotic fractures. While yielding a set of measurements and information related to compromised health in the elderly, the project will also assist in the development of appropriate intervention strategies to avert loss of function in this subject population Award Amount: \$49,472

### Alcohol Abuse/Alcoholism

Alcohol Use/Aging

Title: Alcohol Effects in Postmenopausal Women NIAAA

PI: Judith S. Gavaler, Ph.D., Oklahoma Medical Research Foundation,

Oklahoma City, OK

Key Words: alcohol use, postmenopausal women, estrogens

This supplement will fund the recruitment of additional women into the ongoing study in order to examine ethnic/nationality differences in endocrine status in response to alcohol. The services of a research nurse will be required to assist with recruitment, interviews, and blood drawing. Award Amount \$50,000

### Alcohol Abuse/Behavior

► Title: A Prospective Study of Offspring of Alcoholics NIAAA

PI: Kenneth Sher, Ph.D., University of Missouri, Columbia, MO Key Words: alcohol abuse, sexual and physical abuse, paternal alcoholism

Supplemental funds will make possible the addition of new questions to the data collection instruments and interviews that make possible the investigation of paternal alcoholism as a risk factor for sexual abuse, physical abuse, and neglect. It will also assess the extent to which a history of abuse (especially sexual) predisposes subjects to alcohol abuse/dependence. Award Amount. \$37,911

### Alcoholism

► Title: Naltrexone Treatment of Alcohol Dependence NIAAA

PI: Joseph R. Volpicelli, M.D., Ph.D., University of Pennsylvania,

Philadelphia, PA

Key Word: alcoholism, naltrexone, behavior

Supplemental funds will help develop a valid screening instrument to detect and diagnose trauma-associated psychopathology in alcoholic women. A secondary goal will be to use this instrument to identify subgroups of alcohol-dependent women diagnosed as having dissociative or post-alcohol relapse. The PI will also assess the change in trauma-associated symptoms as a function of naltrexone treatment. Award Amount. \$100,000

### Alcoholism

► Title: Human Alcohol and Aldehyde Dehydrogenases NIAAA

PI: Ting-Kai Li, M.D., Indiana University School of Medicine,

Indianapolis, IN

Key Word: gastric emptying, Chinese women and men, menstrual cycle

This supplement proposes to measure gastric emptying of alcohol followed by assessment of first past metabolism in Caucasian women and men and Chinese women and men. In addition, investigations into the gastric emptying rate of alcohol in the follicular and luteal phase of the menstrual cycle of women will be pursued. Award Amount: \$50,000

### Alcoholic Drinking Behavior/Behavior

► Title: Naltrexone and Cognitive Behavior Therapy of Alcoholism NIAAA

PI: Raymond F. Anton, M.D., Medical University of South Carolina,

Charleston, SC

Key Words: post-traumatic stress disorder, naltrexone

The primary aim of this supplement is to explore whether alcoholic women with post-traumatic stress disorder (PTSD) will have a differential response to treatment of their alcohol dependence when compared to women without PTSD and to examine whether naltrexone, when added to cognitive behavioral therapy, improves their response. Award Amount: \$99.849

### Alcohol Use/Behavior

► Title: Assessment of Rural Adolescent Alcohol Use NIAAA

PI: Kelly Kelleher, M.D., M.P.H., Ark Children's Hospital Research

Center, Little Rock, AR

Key Words: rural and urban adolescent females, depression, alcohol consumption

This supplement will allow a significant increase in the sample of adolescent females, especially in rural areas. This will help determine whether adolescent females from two distinct rural regions differ from each other or from urban adolescent females in their rates of drinking and in frequency of depression and comorbid problem drinking. It will also allow a comparison of school survey data and telephone data collection methods for self-reported alcohol consumption among adolescent females. Award Amount: \$49,997

### Alcoholism/Behavior

► Title: Family versus Behavioral Treatment of Alcoholism NIAAA

PI: Larry E. Beutler, Ph.D., University of California, Santa Barbara, CA

Key Words: behavior, treatment, family

Historically, most studies of alcoholism have involved male samples and have assumed that the findings would be applicable to females. However, various reports have challenged this assumption. Supplemental funds will help to: (1) revise and refine the treatment manuals to fit female index cases, (2) pilot-test recruitment strategies to bring female alcoholics and their spouses to treatment, (3) pilot-test the efficacy of the modified manuals, and (4) generate hypotheses regarding subgroups of female alcoholics. Award Amount: \$100,000

### Behavioral Studies

**Smoking Cessation** 

► Title: Southeast Asian Women: Their Smoking and Passive Smoking NHLBI PI: Moon S. Chen, Ph.D., M.P.H., Ohio State University, Columbus, OH

Key words: smoking, behavior, Southeast Asian women

Supplemental funds will initiate and evaluate lay-led smoking cessation intervention for Southeast Asian Women. This will permit longitudinal quantilication of the exposure not only to active smoking but also to passive smoking among nonsmoking Southeast Asian women. Award Amount: \$76,758

Eating Disorders

Title: Risk Factors for Unhealthy Weight Regulation NICHD

PI: C. Barr Taylor, M.D., Stanford University Medical School,

Stanford, CA

Key Words: eating disorders, prevention, Hispanic, African-American students

The study will expand its investigation of risk factors associated with unhealthy weight regulation in adolescent females and develop preventative treatments by increasing the number of African-American students and adding a cohort of Hispanic students. (The original cohort comprises Asian women.) The supplement will locus on determining the course of eating disorder symptoms in Hispanic high school females. Award Amount. \$100,000

### Stress

► Title: Caregivers of AD Victims Stress and Mental Health NIMH
PI: Janice K. Kiecolt-Glaser, Ph.D., Ohio State University, Columbus, OH
Key Words: chronic stress, endocrine and immune changes

Caregiving for an elderly parent or spouse has become a common phenomena in our society. In many ways, caregiving for an individual with Alzheimer's disease (AD) is a natural paradigm for studying the effects of chronic stress on the health and mental health of the caregiver. A cohort of 40 women will be examined to intensively assess basal- and stress-provoked hormone profiles and cellular immunity, and to examine the degree to which enhanced catecholinergic reactivity to a mental stressor produces exaggerated endocrine and immune changes. The study will examine how social and behavioral factors shape age-related differences in cardiovascular reactivity, how differences in reactivity are related to neuroendocrine and immune responses, and how individual differences in cardiovascular reactivity relate to degree of immune reactivity and immunological memory to vaccination. The findings from this supplement will help elucidate our understanding of how older women are physiologically and psychologically affected by chronic stress. Award Amount. \$50,000

Eating Disorders

➤ Title: Do Food Deprivation and Mood Influence Binge Eating? NIMH
Pl: W. Stewart Agras, M.D., Stanford University, Stanford, CA

Key Words: bulimia nervosa, binge eating disorder

Supplemental funding will permit the addition of a bulimia nervosa group to a one-year study of food deprivation so that responses of individuals with binge eating disorder and bulimia nervosa can be compared. Award Amount: \$45,162

Maternal Employment

► Title: Nursing: Maternal Employment and LBW Infant Outcomes NINR

PI: Joanne Youngblut, Ph.D., R.N., Case Western Reserve University,

Cleveland, OH

Key Words: maternal employment, single-parent families, minority families

One hundred and twenty single-parent families will be added to the research group to enable investigators to: (1) address major gaps in knowledge about the context, determinants, and effects of maternal employment in female-headed, single-parent families; (2) provide information about the effects of different family life courses; and (3) increase representation of minority families and reduce racial bias. The design of the parent grant groups will not provide valid information without this recruitment. Separate and comparative analyses of this group will increase the generalizability of the study. Award Amount: \$99,998

Work Injury and Disability

► Title: Work Injury and Disability: Gender, Health Care, and Outcome NIAMS

PI: David A. Fox, M.D., University of Michigan, Ann Arbor, MI

Key Words: occupational injuries, disability, gender

The supplement provides funding to access and extract information from a large occupational injury database. Patterns among various clinical variables will lead to identification of case management decisions based on gender differences. The outcome will be relevant to health issues by virtue of ascertaining the role gender plays in the outcome of work injuries and disability. Award Amount: \$50,000

### Cancer

Basic Research: Breast Cancer

► Title: Progesterone Receptors in Breast Cancer NCI

PI: Kathryn B. Horwitz, Ph.D., University of Colorado, Denver, CO

Key Words: cancer, reproductive endocrinology

This project addresses basic molecular mechanisms underlying the actions of antiprogestin-occupied progesterone receptors. Previous studies have discovered the possibility that, by manipulating the cellular environment, these hormones can switch between antagonist and agonist activity. This is a change in the view of the way steroid receptors function. The supplement provides funds to extend work into areas that have important implications for reproductive endocrinology and contraception by focusing on cell-specific, receptor-specific, and even gene-specific differences in transcriptional responses to these agents. The studies also have implications for drug design. Award Amount: \$100,000

### Genetic Research

► Title: Growth Control in Aging Fibroblasts NIA

PI: Eugenia Wang, Ph.D., Lady Davis Institute for Medical Research,

Montreal, Quebec, Canada

Key Words: gene expression, tumor suppression, cell proliferation

This supplement will identify abnormal expression of "predisposing genes" for women at risk of developing colon and uterine cancer. It is hypothesized that these "at risk" women already have mutations affecting one or two of the five or six molecular steps required for cancer development and that initial hits occur in genes directly involved in regulating cell proliferation. Messenger RNA levels corresponding to several cell cycle-dependent genes in tumors and transitional zones between tumors and normal tissue will be characterized. Outcome is a predictive tool for early detection of women at risk for colorectal and uterine cancer. Award Amount: \$81,074

Cervical Dysplasias

► Title: Cervical Dysplasias in Ethnic/Minority Subgroups

PI: Seymour L. Romney, A.B., M.D., Albert Einstein College

of Medicine, Bronx, NY

Key Words: cervical cancer, chlamydia trachomatis

This supplement will test the hypothesis that infection with chlamydia trachomatis represents an independent risk factor for the development of cervical neoplasia.

NCI

Award Amount, \$49,893

Lung Cancer

► Title: Committee on Women's Health-Lung Ancillary Studies NCI

PI: Charles A. Coltman, Jr., M.D., Cancer Therapy and Research Center,

San Antonio, TX

Key Words: lung cancer, smoking, behavior

This supplement will be used to support ancillary studies in lung cancer. Specific aims include to: (1) perform a multivariate analysis on an expanded lung cancer database that will address the questions of gender differences and smoking patterns raised in earlier research and propose questions for prospective study, (2) develop an ancillary questionnaire to be used longitudinally with two new lung cancer trials to address the impact of smoking patterns and other behaviors on long-term survival and second primary cancers; (3) research appropriateness of and devise a pilot study for a novel smoking intervention trial in women potentially cured of their first malignancy. Award Amount: \$50,000

Lung Cancer

► Title: Spermidine N1-acetylase Induction in Lung Cancers NCI PI: Robert A. Casero, Ph.D., The Johns Hopkins University, Baltimore, MD

Key Words: anticancer agents, spermidine/spermine NI-acetyltransferase gene,

lung cancer

The gene for spermidine/spermine N1-acetyltransferase (SSAT) has been localized on the human X chromosome. This suggests that it may be regulated differently in males and females and that male and female tissues may show differences in responsiveness to the bis(ethyl)polyamine class of anticancer agents. This supplement will determine if there are sex-related factors that alter lung tumor and normal lung tissue responsiveness to this new class of agents. It will also focus on studying patterns of methylation in male and female tissues that could provide new insight into the regulation of the expression of SSAT. Award Amount: \$100,000

### Treatment and Prevention

► Title: Correlative Studies in Women with Unresectable Meningioma NCI

PI: Charles A. Coltman, Jr., M.D., Southwest Oncology Group,

San Antonio, TX

Key Words: RU486, therapy, meningioma

This supplement will increase the database on RU486 therapy for meningionias with analysis of endocrine parameters in patients treated for periods up to five years and after discontinuation of RU486 therapy, using serum samples obtained during the pilot phase of the current parent grant. Award Amount: \$100,000

NCI

#### Cancer Prevention

► Title: National Network for Hispanic Cancer Prevention

PI: Amlie G. Ramirez, Dr.P.H., University of Texas Health Science Center.

San Antonio, TX

Key Words: cancer prevention, sexual behavior, HPV, violence, Hispanic/Latina women

The parent project is a cancer prevention study that assesses multiple cancer risks and preventive behaviors among Hispanic/Latinas of different origins and backgrounds. The data will lead to the design of a community intervention program to reduce cancer morbidity and mortality. The supplemental funds will expand data collection to assess the sexual practices prevalent among Hispanic/Latina women and how they may increase their risk for contracting sexually transmitted diseases including human papillomavirus, which has been found to be associated with cervical cancer. Additional data will be collected on domestic violence. Award Amount: \$74,456

#### Cancer/Health Promotion

► Title: Accelerating Worksite Smoking Control Programs NCI

PI: James Prochaska, Ph.D, University of Rhode Island, RI

Key Words: health promotion, behavior, cancer, hard-to-reach women, intervention

Supplemental funds will be used to: (1) identify the conditions that enhance and impede participation in health promotion programming (particularly, nutrition and tobacco control interventions) for hard-to-reach women who work in manufacturing settings, and (2) develop a social marketing strategy for enhancing participation in health promotion programs targeted to the needs and interests of these women. A tracking system that monitors an individual's participation in all worksite intervention activities will be developed. Award Amount: \$33,382

#### Treatment

► Title: Women and Women Minorities in Radioimmunotherapy NCI

PI: John Shively, Ph.D., Beckman Research Institute, CA Key Words: CEA tumors, lung, immunotherapy, minority women

The primary objective of the parent grant is to study the role of radiolabeled, genetically engineered monoclonal antibodies in the treatment/reduction of tumors in colon, rectum, lung, and breast cancer patients. Supplemental funds will be used to expand the recruitment of a minority women patient population for innovative immunotherapy trials in CEA-positive tumors. Specific marketing efforts, including mailings and presentations (with the appropriate language translations) to key groups (i.e., women and minorities in hospitals and medical groups, community physicians, and the media), will be used with the intent of increasing participation of minority women by 50 percent. Award Amount: \$100,000

## Cardiovascular Disease

Pulmonary Hypertension

► Title: Adaptations to Hypoxia NHLBI

Pl: John Weil, M.D., University of Colorado, Health Sciences Center,

Denver, CO

Key Words: hypoxia, genetics, animal model, sex hormones

Supplemental funds will be used to study the gender differences in an animal model of primary pulmonary hypertension by examining the genetic determinants and the influence of sex hormones. Award Amount: \$100,000

Coronary Heart Disease

Title: Follow-Up of the 1985-86 NHLBI PTCA Registry

NHIRI

PΙ· Katherine M. Detre, Dr.P.H., M.D., University of Pittsburgh.

Pittsburgh, PA

Key Words: balloon angioplasty, women

This supplement will support recruitment of 500 consecutive women treated with balloon angioplasty and will collect data and begin analysis of observed outcomes and follow-up. Comparison of present outcomes with outcomes from 1985-86 will provide information on whether this technology has changed specifically for women and impacted women's health Award Amount: \$50,000

Coronary Heart Disease

Post-Protamine Complement Activation in Cardiac Surgery NHI BI Title:

PI: Shastri A. Kaushikkumar, M.D., VA, Research Foundation of

SUNY, Buffalo, NY

Key Words: coronary bypass grafting, premenopausal women

Supplemental funds will be used to further understand the pathophysiologic reasons for gender differences in the efficacy of coronary artery bypass grafting. Studies will focus on: (1) the effect of body surface area and coronary vessel size on post-operative morbidity, (2) the effect of gender on susceptibility to compliment activation by heparin-protamine complexes in vitro, and (3) the effect of gender on in vitro studies of neutrophil adhesiveness to cultured human endothelial cells in the presence or absence of heparin and/or protamine and/or human sera. Premenopausal women will be included during various phases of their estrous cycle in aims two and three. Award Amount \$48,378

Coronary Heart Disease

Follow-Up of the 1985-86 NHLBI PTCA Registry NHLBI Title:

PΙ· Katherine M. Detre, Dr.P.H., M.D., University of Pittsburgh,

Pittsburgh, PA

Key Words: angiography assessment, gender differences

Supplemental funds will support the expansion of the analysis of women by performing detailed angiographic assessment of the arteriograms of women. This detailed evaluation will help identify gender differences based on anatomic and morphologic descriptors. Award Amount; \$50,000

Hypertension

Title: Epidemiology of Lead, Diet, and Blood Pressure **NIEHS** 

PI: Howard Hu, M.D., Channing Laboratory, Boston, MA

Key Words: lead exposure, hypertension, women

Supplemental funds will be used to study the effects of low-level lead exposure on blood pressure in women. Evaluation of bone lead stores in women is important to also understand target organ damage for diseases such as osteoporosis. Award Amount: \$49,999

## Depression

Cognition

► Title: Negative Cognition Depression: Etiology and Course NIMH

PI: Lauren B. Alloy, Ph.D., Temple University, Philadelphia, PA

Key Words: depression, young women, gender differences

Supplemental funding will permit the investigators to address four questions important to women's health: (1) Do young women exhibit higher rates of differential manifestation of depression than young men?, (2) Do young women and, in particular, women of color exhibit greater psychological vulnerability for depression than young men?, (3) Do developmental experiences predict young adult levels of cognitive risk for depression and rates of depression?, and (4) Do gender differences in developmental experiences predict gender differences in young adult cognitive risk for, and rates of, depressive disorders? Award Amount: \$100.000

## **VLBW Mothers**

► Title: Mothers—VLBW Infants: Anxiety Depression Immune Response NINR PI: Susan Gennaro, D.S.N., University of Pennsylvania, Philadelphia, PA

Key Words: retention, depression and health, African-American women

Researchers have found that poorer, undereducated, minority women are most likely to drop out of studies because keeping contact with these women is difficult because they move often, do not always have functional phones, and do not always get their mail. Supplemental funds will be used to expand techniques that have been successful in the past to ensure that women only drop out of this longitudinal study because they do not wish to participate, not because of keeping contact. The study examines anxiety, depression, health habits, and immune functioning in mothers of very low birthweight infants and mothers of healthy term infants. The sample will comprise 78 percent urban, African-American women. The supplement will ensure that important information about the health habits of the poorest, most at-risk women will be obtained and that a high recruitment and retention rate would be maintained. The project has a focus on depression and health and special attempts to retain African-American women in the study. Award Amount: \$40,944

#### Risk Factors

► Title: Depressed Children Grown Up: Children at High and Low Risk

for Depression NIMH

PI: Myrna M. Weissman, Ph.D., Research Foundation for

Mental Hygiene, NY, NY

Key Words: depression, intervention

This supplement will determine barriers women have in receiving adequate treatment; will determine their perception of the diagnostic needs, social needs, school problems, and treatment needs of the next generation; and will obtain direct preliminary data on the third generation. It will offer the opportunity to gain insight into how the cycle of depression may be broken by education and treatment, and whether there are differential manifestations, periods, situations, and risks in men and in women. Award Amount: \$99,963

# Developmental/Reproductive Biology

Mammary Gland

► Title: Physiological Factors Affecting Human Lactation

NICHD

PI:

Margaret C. Neville, Ph.D., University of Colorado Health,

Denver, CO

Key Words: lipoprotein lipase, mammary gland, lactation, breast cancer

This supplemental funding will permit the development of an *in vitro* model system (a milk-producing mammary culture system) that would allow the study of basic biology of the mammary gland. Award Amount. \$50,000

Basic Research: Antiprogestin/Menstrual Cycle

► Title: Hormonal Control of the Female Reproductive Tract NICHD

PI: Robert M. Brenner, Ph.D., Oregon Primate Research Center,

Beaverton, OR

Key Words: unopposed uterine bleeding, RU486, primate model system

The supplement will use the rhesus monkey as a model system to study the hormonal mechanisms that regulate periodic changes that occur in the reproductive tract of female primates during the menstrual cycle. This study will examine the effects of RU486 on unopposed estrogen action of the female reproductive tract and possible use of RU486 for treatment of unopposed uterine bleeding caused by estrogen. Award Amount. \$50,000

#### PMS/Behavior

► Title: Nursing Assessment of PMS: Neurometric Indices NINR

PI: Ora Lee Strickland, Ph.D., Emory University, Atlanta, GA Key Words: PMS, depression, recruitment, African-American women

Supplemental funds will be used to increase the participation of minority women, particularly African-American women, from 19 percent to 35 percent, in an ongoing study of perimenstrual symptoms. Neurometric function assessment through neurometric analysis will be used to validate and provide a greater understanding of perimenstrual symptoms. The study focuses on depression, health, and the recruitment/retention of minority subjects. Award Amount: \$84,353

Lupus/Pregnancy

► Title: Epidemiology of Reproductive Outcome in Lupus NIAMS

PI: Richard M. Pope, M.D., Northwestern University, Evanston, IL Key Words: immunosuppressive drugs, lupus, pregnancy, African-American women

The focus of the current funded project is to identify patients for the Chicago Lupus Database, complete database forms containing clinical and laboratory information pertinent to systemic lupus erythematosus (SLE), document previous pregnancy outcomes by patient interview and review of obstetrical records, and provide a retrospective assessment of the interaction of immunosuppressive drugs on pregnancy outcome in lupus patients. Supplemental funds will be used to assess specifically pregnancy outcomes in African-American women. Award Amount: \$100.000

# Digestive Disorders

Irritable Bowel Syndrome

Title: Psychophysiology of IBS

NIDDK

PI:

William Whitehead, Ph.D, Johns Hopkins University School of

Medicine, Baltimore, MD

Key Words: irritable bowel syndrome, pathophysiology, hysterectomies

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder among women. Women with IBS are three times more likely to have a hysterectomy compared to women without IBS. Unfortunately, the hysterectomy usually does not relieve the symptoms of IBS. Supplemental funds will be used to confirm hypotheses that will aid in the understanding of the pathophysiology and the mechanisms of IBS and could be instrumental in preventing a number of hysterectomies. Award Amount: \$100,000

# Drug Abuse

## Treatment/Behavior

► Title: Buprenophine Maintenance for Opioid Addicts

NIDA

PI: Thomas Kosten, M.D., Yale University, New Haven, CT

Key Words: post-traumatic stress disorder, comorbid depression, women, recruitment

The supplement will provide the opportunity to recruit women subjects who are on a list to enter methadone maintenance programs. Patients will all be examined for post-traumatic stress disorder (PTSD) and lifetime and current risk behaviors, including sexual behaviors. The analysis of data will include correlation of treatment efficacy with the severity of comorbid depression and PTSD. Award Amount: \$99,901

#### Gender Differences

► Title: Cocaine/Ethylcocaine Metabolism and Behaviors

NIDA

PI: William Bosron, Ph.D., Indiana School of Medicine, Indianapolis, IN

Key Words: alcohol and cocaine co-abuse, metabolism, women

The study will examine gender differences in the distribution of key cocaine metabolites after co-administration of alcohol and cocaine. The tissue distribution of cocaine esterases and ethyl ester transferases will be studied. Data would fill in gaps in knowledge regarding gender-specific differences in the pattern of cocaine and alcohol co-abuse and in the cocaine metabolism in women. Award Amount: \$50,000

#### Treatment

Title: Carbamazepine Treatment in Cocaine Abusers: Victimization

in Cocaine-Dependent Women NIDA

PI: Kathleen Brady, M.D., Medical University of South Carolina,

Charleston, SC

Key Words: post-traumatic stress disorder, comorbidity, carbamazepine, women

The recruitment of women will be enhanced and the retention will be extended by ninemonth follow-up visits. The supplement will test the hypothesis that carbamazepine might be more effective for women cocaine addicts suffering from post-traumatic stress disorder than for those without the disorder. Award Amount: \$99,703

#### Prevention/Behavior

► Title: Multi-Ethnic Drug Abuse Prevention Among New York Youth NIDA
PI: Gilbert Botvin, Ph.D., Cornell University Medical College, Ithaca, NY

Key Words: prevention, risk factors, adolescent girls

The supplement will expand the parent grant by collecting additional data and expanding data analysis plans in the identification and prevalence of risk factors for tobacco, alcohol, and drug abuse among African Americans and Hispanics (adult and adolescent women). The responsiveness of women to preventive interventions targeting tobacco, alcohol, and drug abuse will also be evaluated. The investigators will look at the effectiveness of the life skills training using multi-ethnic (including 5 percent Asian) adolescent girls in housing projects, schools, and homeless family shelters. Award Amount \$99,579

#### Endocrine Disorders

## Diabetes Mellitus

► Title: Japanese-American Community Diabetes Study NIDDK

PI: Wilfred Y. Fujimoto, M.D., University of Washington

School of Medicine, Seattle, WA

Key Words: noninsulin-dependent diabetes mellitus, menopause, Japanese-

American women

The parent grant has established that noninsulin-dependent diabetes mellitus (NIDDM) is highly prevalent among Japanese-American women, particularly in relation to the prevalence of NIDDM in Japan. The supplemental funds will be used to compare the risk of NIDDM in third generation Japanese-American women with first and second generation Japanese-American women. Supplemental funding will enable more exhaustive medical histories to be included in follow-up study interviews. Award Amount: \$97,867

#### Genetics

## Genetic Diseases in Women

► Title: Mouse Mutant Gene Resource NCRR

PI: Muriel T. Davisson, Ph.D., Jackson Memorial Laboratory,

Bar Harbor, ME

Key Words: estrogen, animal model, etrodactyly, cardiomyopathy, mutations

This supplement will support in-depth molecular and pathological analyses of three spontaneous mouse mutations that may provide potential models for research on genetic diseases affecting women. A recessive mutation called male sterility (inster) was recently mapped near the estrogen receptor locus (Estr.). Estr is a likely candidate locus for the mister mutation. A mutation in the estrogen receptor gene would provide a mouse model system for studying diseases, such as breast cancer and osteoporosis, in which estrogen plays a key role. A second mutation, Dac, may help identify the location of one of the human genes causing ectrodactyly, an inherited condition suffered by women. A third mutation that causes cardiomyopathy has also been identified. Award Amount: \$50,000

#### Women Carriers

Title: Ornithine Transcarbamylase Deficiency in Women NICHD

PI: Saul W. Brusilow, M.D., Johns Hopkins University, Baltimore, MD

Key Words: ornithine decarboxylase deficiency

This supplement is to determine and measure the consequences of ornithine decarboxylase deficiency in a large population of women carriers of this condition as compared to normal women. This will achieve a statistical power that will detect differences between carriers and non-carriers. Award Amount: \$100,000

# Maternally Transmitted Deafness

► Title: Molecular Basis of Maternally Transmitted Diseases NIDCD

PI: Nathan Fischel-Ghodsian, M.D., Cedars-Sinai Medical Center,

Los Angeles, CA

Key Words: maternally transmitted deafness, ototoxicity

The supplement will address the identification of carriers of maternally transmitted sensitivity for aminoglycoside-induced ototoxicity with the ultimate goal being prevention of this form of deafness. The focus will be the mitochondrial DNA, including a 12S ribosomal RNA gene. Mutations in the latter gene are linked to maternally transmitted deafness, and preliminary studies have shown a similar mutation in pedigrees with familial aminoglycoside-induced ototoxicity. Award Amount: \$50,000

## Basic Research: Adrenoleukodystrophy

► Title: Adrenoleukodystrophy: Studies of Female Heterozygotes NIDDK

PI: Sakkubai Naidu, M.D., Kennedy Krieger Research Institute,

Baltimore, MD

Key Words: adrenoleukodystrophy, X-linked genetic disease, gene mutations

This supplement will identify specific mutations of the gene for adrenoleukodystrophy and will provide further knowledge about the molecular basis of this women's disease. The gene, which is found on the X chromosome, was identified as part of the parent grant. Once identified, specific mutations will be correlated with severity of symptoms in heterozygous females. Award Amount: \$100,000

# Cystic Fibrosis

► Title: Cystic Fibrosis Core Center NIDDK

PI: Pamela B. Davis, M.D., Ph.D., Case Western Reserve University,

Cleveland, OH

Key Words: cystic fibrosis, pulmonary function

Women with cystic fibrosis have a life expectancy of three to five years less than men. This supplement will focus on the potential basis of this gender difference by performing an epidemiological study using patient data derived from the Cystic Fibrosis Center. Specifically, the analysis will determine the extent to which differences in body composition, exercise capability, essential fatty acid metabolism, inflammatory response, and treatment utilization may correlate with the gender gap in survival. Recognition of correlates will enhance our understanding of the etiology of this disease. Award Amount: \$98,269

# Genitourinary/Urologic

► Title: Host Factors in Susceptibility to UTI NIDDK

PI: Anthony J. Schaeffer, M.D., Northwestern University, Evanston, IL Key Words: urinary tract infections, African-American women, Hispanic women

Urinary tract infections (UTI) are the most frequent of all kidney and urologic diseases affecting women and cause significant morbidity and mortality. This supplement will be used to address racial differences that may exist in terms of prevalence, incidence, and recurrence rates of UTI in women. Three racial groups will be compared. African American; Hispanic, and Caucasian, non-Hispanic. Award Amount. \$79,167

# Hormonal

Smoking/Cessation

► Title: Smoking and the Effects of Nicotine in Women NCI

PI: Ovide F. Pomerleau, Ph.D., University of Michigan, Ann Arbor, MI

Key Words: smoking cessation, menstrual cycle, behavior

The purpose of this project is to understand the relation of psychological and physiological aspects of menstrual phase to cigarette smoking. Data collected to date suggest that an underlying dysregulation of the hypothalamic-pituitary-adrenal axis is responsive to hormonal changes that increase nicotine requirements and may be closely linked and similar to the effects of depression. With this supplement, the investigators will attempt to verify biologically this observation and to identify a large cohort for further studies on the effects of smoking on the severity of depression and cortisol levels. Results will provide insight into the characteristics of women who have the most difficulty quitting and will allow tailoring of prevention and cessation strategies to these high-risk women. Award Amount: \$49,990

Basic Research: Disorientation

► Title: Disorientation—Model for Nursing Therapy NINR

PI: Barbara Therrien, Ph.D., R.N., University of Michigan,

Ann Arbor, MI

Key Words: disorientation, animal model, gender differences

The supplemental funds will lay the groundwork for evaluating data that suggest that disorientation in females may be more difficult to manage and treat, and may actually require different therapeutic approaches. This will be done by a timely exploration of the influence of: (1) the estrous cycle, and (2) general activity levels on behavioral performance of large-scale spacial tasks in females. Male and female rats with and without hippocampal damage will be used. Award Amount: \$50,000

Basic Research: Estrogen Therapy

► Title: Porphyrin Biosynthesis in Normal and Disease States NIDDK

PI: J. Kushner, M.D., University of Utah Medical Center,

Salt Lake City, UT

Key Words: estrogen, errors in metabolism, porphyria cutanea tarda (PCT)

The incidence of porphyria cutanea tarda (PCT) has increased among women with the use of oral contraceptives and estrogen replacement therapy in the past three decades. PCT is an inborn error of metabolism. Supplemental funding will be used to establish an animal model to help explain the mechanism of estrogen promotion of clinical PCT and to determine the safety of transdermal estrogen replacement therapy in postmenopausal women previously treated for PCT. Award Amount: \$100,000

# Immunology

Basic Research: Organ Transplant Rejection (Kidney)

Title: Desensitization by Anti-Idiotypic ABS to MHC Class 1
 PI: William J. Burlingham, Ph.D., University of Wisconsin, Madison, WI

Key Words: antigen sensitization, parous females

This supplement will examine the higher frequency of sensitization to the HLA or transplantation antigens in women. The increased occurrence of anti-HLA antibodies results from pregnancy. The investigators will develop reagents that would result in clonal deletion of the cells involved in antibody production focusing on the antibodies found in parous females. They will compare these antibodies to those resulting from transplantation or transfusion. Award Amount: \$50,000

Basic Research: Sepsis

► Title: Mechanisms Mediating Metabolic Changes in Sepsis NIGMS

PI: John Spitzer, M.D., Louisiana State University Medical Center,

New Orleans, LA

Key Words: immune response, estrous cycle, sepsis, rat gender differences

The supplement will provide information on the role of host defense in the dynamic changes elicited by sepsis and will improve understanding of immune response in women. This will be done by looking at host defense mechanisms involving neutrophils and resident macrophages in male rats and female rats at various stages of the estrous cycle and at various points in their life cycle. Award Amount: \$50,000

Systemic Lupus Erythematosus

► Title: Immunologic Mechanisms in Lupus Nephritis NIDDK

PI: Michael P. Madaio, M.D., University of Pennsylvania School of

Medicine, Philadelphia, PA

Key Words: systemic lupus erythematosus, kidney disease, end-stage renal disease,

young women

The parent grant focuses on systemic lupus erythematosus (SLE), a common autoimmune disorder that affects young women. Supplemental resources will be used to enhance the understanding of events occurring at the cellular and subcellular levels. This information in turn will aid in the development of interventions that would result in secondary prevention of SLE complications such as lupus nephritis, or curtail the progression of kidney disease to end-stage renal disease, once the renal injury has occurred. Award Amount: \$100,000

Autoimmunity

► Title: Autoantibodies to Activated Lymphocytes in SLE NIAMS

PI: John B. Winfield, M.D., University of North Carolina,

Chapel Hill, NC

Key Words: SLE (prototype systemic autoimmune disorder), African-American women

The parent grant addresses the identification of a possible linkage between the presence of a heat shock protein gene with the systemic autoimmune disorder, systemic lupus erythematosus (SLE) in African-American women. The purpose of the supplement is to determine the sequence of the heat shock protein allele that is preferentially expressed in SLE patients, as well as survey minority patients for the presence of additional genetic haplotypes. Findings will provide basic information concerning why African-American women are predisposed to SLE and related autoimmune disorders. Award Amount: \$50,000

Rheumatoid Arthritis/Sjögren's Syndrome

► Title: T-Cell Receptors in Rheumatoid Arthritis NIAMS

PI: Chris D. Platsoucas, Ph.D., Temple University School of Medicine,

Philadelphia, PA

Key Words: rheumatoid arthritis, primary Sjogren's syndrome, autoimmune diseases

The parent grant tests the hypothesis that rheumatoid arthritis is an autoimmune reaction brought about by the clonal expansion of T-cells that infiltrate the synovial membrane or extravasate into the synovial fluid. This supplement will permit testing of this hypothesis in a closely related autoimmune disease, primary Sjogren's syndrome, that preferentially affects women. Outcome from the studies will potentially contribute to the design of specific T-cell therapy for arthritis and Sjogren's syndrome. Award Amount: \$50,000

# Osteoarthritis

► Title: Gender Differences in Utilization of Joint Arthroplasty NIAMS

PH: Matthew H. Liang, M.D., M.P.H., Brigham and Women's Hospital,

Boston, MA

Key Words: inflammatory arthritis, patient counseling, elderly women and men

This supplement will evaluate gender differences in patients undergoing elective arthroplasty for advanced osteoarthritis. Specifically, 200 elderly patients will be enrolled in intervention groups, and their reasons for selecting surgical intervention will be examined. Data will provide information about health care decisions in the elderly Award Amount \$49,895

# Osteoarthritis

► Title: A Prospective Study of Ostcoarthritis in Premenopausal Women NIAMS

PI: MaryFran Sowers, Ph.D., University of Michigan School of

Public Health, Ann Arbor, MI

Key Words: osteoarthritis, premenopausal women, bone loss

The overall goal of the parent project is to prospectively measure bone mineral density and specific sex steroids in a population of women spanning the time of menopause. Funding of this supplement will permit additional studies to determine the extent to which these variables relate to joint atypia that may predispose to osteoarthritis and increased risk of bone fractures. Identification of factors that contribute to the onset of these conditions will support our understanding of the loss of functional ability in a significant population of older women Award Amount. \$43,430

#### Infectious Diseases

#### AIDS/Behavior Modification/Behavior

► Title: AIDS and African-American Women: Testing Risk Behavior

Interventions

PI: Loretta S. Jemmott, Rutgers University, Newark, NJ

Key Words: interventions, transmissions; African-American female adolescents

The proposed supplement will add 150 adolescents younger than 18 to the original cohort to identify and test cost-effective, culturally sensitive interventions to prevent the transmission of HIV in inner-city. African-American women of childbearing age Behavioral factors, disease risk, sexual behavior, and health will be addressed. An additional minority sample will be recruited. Award Amount: \$100,000

## AIDS/Wasting Disease

► Title: Anabolic Therapies and their Metabolic Effects in AIDS NIDDK

PI: Morris Schambelan, M.D., San Francisco General Hospital,

San Francisco, CA

Key Words: body composition, lipid metabolism, wasting, adult women and AIDS

This supplement is designed to monitor the progression and manifestations of HIV disease in women by investigating fundamental differences in body composition and lipid metabolism in AIDS-infected adult women compared to men. Cross-sectional and longitudinal studies of body composition, energy and substrate metabolism, and nutrient intake in HIV-positive and HIV-negative women will be used. These gender-based differences may affect women's responses to AIDS and lead to potential therapies to attenuate the wasting associated with AIDS. New techniques for recruitment of HIV-positive minority women will be addressed. Award Amount: \$99,405

# AIDS/Postnatal

► Title: Cellular Immunity to HIV in Mothers and Infants NIAID

PI: Susan Plaeger-Marshall, Ph.D., Department of Pediatrics,

Los Angeles, CA

Key Words: pregnancy, postnatal, HIV-infected women

The proposed research will determine the effects of pregnancy on the postnatal course of HIV infection. This proposal would extend the follow-up of the women from 3 months to 2 years, with additional sampling at 6, 12, 18, and 24 months postpartum. The specific aims include: (1) characterization of postnatal changes in the women's T-cell activation as reflected in cell surface phenotype and secretion of cytokines and serum activation markers, (2) determination of postpartum changes in the women's viral burden using quantitative co-culture and PCR, and (3) assessment of the exacerbation of disease as monitored by shedding of virus and production of HIV-specific antibody in cervical secretions. Award Amount: \$98,883

#### AIDS/Clinical Trials/Behavior

► Title: Adult, AIDS Clinical Trials Unit NIAID

PI: Gerald Friedland, M.D., Yale University, New Haven, CT

Key Words: intervention therapy, recruitment, adherence, retention, AIDS clinical trials

This supplement proposes to expand and increase the scientific rigor of ongoing studies regarding recruitment, adherence, and retention in AIDS clinical trials. The supplemental funding will permit expansion of sample size and include a comparison group, thus increasing the statistical power of the research. Award Amount: \$100,000

## AIDS/Behavioral Interventions/Behavior

► Title: Secondary Prevention with HIV-Positive Youths in SF, LA, and NYC NIDA

PI: Mary Jane Rotheram-Borus, Ph.D., Research Foundation

for Mental Hygiene, Inc., New York, NY

Key words: behavioral intervention, HIV-positive youth

The goals of this project are to eliminate and/or reduce substance use and sexual risk acts that transmit HIV and to enhance health care behaviors among HIV-positive youths. Supplemental funding will be used to evaluate the impact of changing females' HIV risk acts on social, emotional, and behavioral adjustment (and physical health of females). Gender differences among HIV-positive youths will be addressed. Award Amount: \$98,691

Candidal Vaginitis

► Title: Vaginotropic and Vaginopathic Strains of Candida Albicans NIAID
PI: David R. Soll, Ph.D., University of Iowa, Iowa City, IA

Key Words: candidal vaginitis, women

The supplement will extend molecular epidemiological studies to characterize the transmission of vaginotropic strains of C albicans throughout the population. Novel data show the natural history of recurrent vaginal candidiasis begins with the woman first infecting a sexual partner who then reinfects her with the same vaginopathic strain. The male partner does not develop the disease. Award Amount: \$100,000

# Neurology

## Metabolic Disorders

► Title: New Amino Acid Disorders in Gerebral Disease NINDS

PI: Vivian Shih, M.D., Massachusetts General Hospital, Boston, MA

Key Words: metabolic disorders, pregnancy outcomes

The parent grant addresses women with inborn metabolic disorders (e.g., isovaleric acidemia, maple syrup urine disease, and propionic acidemia) who, with diet therapy and monitoring, have uncomplicated pregnancies. The supplement has three parts. (1) mechanisms that will allow young women to monitor and assess their own diets will be explored, (2) women with galactosemia will be studied to assess risk for atherosclerosis, cardiovascular disease, and osteoporosis, and (3) pregnancy outcome in women with pyridoxine nonresponsive homocystinemia will be assessed. Award Amount. \$95,715

Basic Research: Epilepsy

► Title: Carbamazepine in Pregnancy NINDS

PI: Joan Lockard, Ph.D., University of Washington, Seattle, WA

Key Words: epilepsy, pregnant monkeys, carbamazepine

The supplement will provide basic research information for the treatment of pregnant women with epilepsy. Studies will be undertaken to evaluate appropriate AED dosages for maternal seizure treatment and will evaluate the teratogenicity of carbamazepine. Award Amount. \$49,734

# Obesity

#### Metabolic Disorders

► Title: Metabolic Rate and Protein Turnover in Obesity NIDDK

PI: John M. Amatruda, M.D., Yale University, New Haven, CT

Key Words: obesity, insulin, lipoprotein lipase, anti-proteolytic effects, noninsulin-

dependent diabetes mellitus, African-American women

This project is designed to determine if reduced obese subjects are at a metabolic disadvantage with regard to subsequent weight gain at "normal" calonic intake, and to investigate insulin responsiveness among the study subjects. The supplement will support the inclusion of stable isotope studies to evaluate further the mechanism behind insulin resistance and its relationship to the etiology of obesity in women. Both African-American and Caucasian obese women will be included to broaden the scope of what is known about minority and gender differences relating to the development of obesity and NIDDM. Award Amount: \$100,000

**NIDDK** 

Food Intake Control

► Title: Food Intake Control by Cholecystokinin in Humans

PI: Harry R. Kissileff, Ph.D., St. Luke's/Roosevelt Hospital Center,

New York, NY

Key Words: cholecystokinin, food intake, gender differences

The supplement will fund studies examining women's feelings and disposition while they are eating. Such considerations are based on evidence that food intake may be controlled by both psychological as well as physiological mechanisms potentially mediated by cholecystokinin. Heretofore, most work with regard to cholecystokinin's role has been done on men. The supplement will ascertain and delineate gender, cultural, and ethnic differences in the control of food intake. Award Amount: \$98.516

Osteoporosis: Bone Metabolism

► Title: Skeletal Homeostasis in Blacks and Caucasians NIAMS

PI: May Parisien, M.D., Regional Bone Center, Helen Hayes Hospital,

West Haverstraw, NY

Key Words: bone metabolism, osteoporosis, African-American women

The parent grant investigates the differences in bone metabolism between African-American and Caucasian women. Both comparative and normative data are used to help determine patterns of bone loss and risk factors unique to osteoporosis. This supplement will be used to enhance the recruitment of African-American women. Award Amount: \$99,621

## Bone Disease

► Title: Validation of Biomarkers for Bone Disease in Racially/Ethnically

Diverse Populations NIAMS

PI: Caren Gundberg, Ph.D., Yale University School of Medicine,

New Haven, CT

Key Words: bone disease, osteocalcin, bone metabolism, racially/ethnically diverse

women and men

Supplemental funds will expand the parent grant to validate osteocalcin as a serum marker for bone disease. The current funds allow the comparison of assays for bone metabolism using either osteocalcin or bone specific alkaline phosphatase. A more thorough evaluation of each of these markers in relation to skeletal disease in different racial and ethnic groups will provide important diagnostic tools necessary to mount the most appropriate medical intervention. Award Amount: \$39,524

#### **Pharmacokinetics**

Basic Research: Drug Metabolism

► Title: Pharmacokinetics/Pharmacodynamics NIGMS

PI: Leslie Z. Benet, Ph.D., University of California, San Francisco, CA Key Words: pharmacokinetics, drug metabolism, immunosuppressive drugs

The supplement will define and characterize the pharmacokinetics and metabolism of immunosuppressive drugs, especially the enzymatic processes involved in drug metabolism. The hypothesis that drug clearance for certain drugs is lower for postmenopausal women than for premenopausal women due to the decrease of the cytochrome P450 enzyme will be tested. In addition, the supplement will investigate the effect of estrogen replacement therapy containing progestational agents on restoring premenopausal levels of enzymatic activity. Award Amount: \$50,000

Drug Metabolism

► Title: Determinants of Individual Responsiveness to Drugs

Grant Wilkinson, Ph.D., Vanderbilt University, Nashville, TN

NIGMS

Key Words: drug metabolism, gender differences, P4503A enzyme action

The supplement will enable investigation of gender differences in the metabolism of drugs subject to degradation by P4503A enzyme. To accomplish this, a test will be developed to account for gut and liver metabolism and to validate results obtained previously from the erythromycin breath test. An additional component will include females evenly divided between those taking and those not taking birth control medication to look at the effect of ethinyestradiol and other medications normally metabolized by P4503A. Award Amount. \$100,000

## Violence

# Antisocial Behavior

► Title: Antisocial and Violent Behavior—Longitudinal Sequelae NIMH

PI: Robert B. Cairns, Ph.D., University of North Carolina,

Chapel Hill, NC

Key Words: antisocial behavior disorders, African-American women,

Euro-American women

This supplement will focus on the intergenerational relationships between antisocial behavior disorders in parents and offspring. It will also enhance understanding of the physical and mental health of African-American and Euro-American women by increasing the sample size of minority women subjects. This work will extend the 12-year Carolina Longitudinal Study. Award Amount: \$49,997

## Childhood Abuse

► Title: Across Generations: Family Life and Mental Health NIMH

PI: Stuart T. Hauser, Ph.D., Massachusetts Mental Health Center,

Boston, MA

Key Words: childhood abuse, marital relationships

The supplement supports research examining the relationship between reports of early childhood abuse/trauma and women's current psychological functioning and marital relationships. The wives of male subjects who reported abusive experiences will also be compared with wives of men who did not report such experiences. All women will participate in extended psychiatric interviews to assess personality disorders and post-traumatic stress disorder. Award Amount: \$100,000.

#### Post-Traumatic Stress Disorder

► Title: Incest Survivors with PTSD: A Comprehensive Treatment NIMH

Pl: Jonathan R. Davidson, M.D., Duke University Medical Center,

Durham, NC

Key Words: incest, abuse, fluoxetine

This supplement extends the parent treatment grant by adding a sample of incest survivors, through an extension of a 12-month fluoxetine protocol currently being applied with rape victims. With this addition, comparisons can be made of the efficacy of the 12-month fluoxetine treatment for sexual trauma survivors, with and without a history of incest, as well as provide pilot data evaluating the relative effectiveness of fluoxetine (Prozac) versus fluoxetine plus psychotherapy in the incest group. Award Amount: \$48,485

Post-Traumatic Stress Disorder

► Title: Mini-Structured Clinical Interview for DSM-III-R

Dissociative Disorder NIMH

PI: Marlene Steinberg, M.D., Yale University, New Haven, CT

Key Words: trauma, Hispanic women, dissociative symptoms

The Mini-SCID-D, which incorporated DSM-IV criteria, was developed to screen for patients suffering from post-traumatic and dissociative symptoms. Supplemental funds will permit reinstatement of the full complement of subjects, allowing the richness of the database to be fully explored. Furthermore, these funds will enable the PI to hire bilingual and bicultural interviewers, trained to evaluate Hispanic patients, and process them through the entire protocol. To date, there have been no published studies of systematic assessment of post-traumatic dissociative symptoms or histories of trauma in Hispanic women. Award Amount: \$50,000

#### Sexual Abuse

► Title: Cognitive Processing of Traumatic Sexual Victimization NIMH

PI: Mary P. Koss, Ph.D., University of Arizona, Tucson, AZ

Key words: rape, Chicana and Navajo women

This supplement adds two additional goals to the parent grant: the examination of cognitive strengths cross-culturally, and the documentation of intrusive memories using an innovative research technique (diary methodology). It will enhance recruitment of minority women into the research such as Chicana and Navajo rape victims in Arizona. Award Amount: \$100,000



# FY 1994 ORWH RESEARCH SUPPORT

- ► Special Research Initiatives
- ► Targeted Research Initiatives
- ► Administrative Supplements to Ongoing Research Grants

# FY 1994 SPECIAL RESEARCH INITIATIVES

# ► Title: Multiple Roles of Middle Generation Caregiving Women NIA

This research examines how well middle generation women, aged 35 to 55 years, who simultaneously occupy multiple roles (e.g., primary caregiver, mother, wife, and employee), adapt to the demands of these multiple roles and how these roles influence women's psychological, social, and physical well-being over time. The effects of stress and role support on women's well-being and whether these processes affect the caregiver role will be examined. Changes in well-being and the effect of role mastery as a mediator in stress, support, and well-being will be examined. The impact of role change will be evaluated in terms of the nature, type, and prior role quality. Three face-to-face interviews will be conducted with 280 women at 12-month intervals. Award Amount: \$132,397

# ► Title: Risk Factors for Physical Disability in Aging Women NIA

The two goals of this longitudinal observational study are: (1) to identify early decrements in physical functioning in women 65 years and older and to demonstrate whether these changes predict future disability, and (2) to evaluate the diseases considered to be risk factors for the onset of preclinical disability and progression to full disability and dependency. The study population of 600 women, 70 to 79 years of age, will be drawn from the Women's Health and Aging Study. The longitudinal observational study will evaluate physical function, including performance-based measures of preclinical and clinical disability; health status, including disease-based and physiological changes of aging; and potential modifiers of function, including cognition, education, and psychosocial function. Cross-sectional and longitudinal analysis of the natural history of preclinical disability, the development of disability, and the risk factors for changes in functional status will help to better define those older women at greatest risk of disability and potential risk factors that could be used to develop effective interventions to prevent disability in aging women. Award Amount: \$235,000

# ► Title: Sexual Dimorphism of the Immune System in Sepsis and Traumatic Injury NIGMS

The purpose of this research is to investigate gender differences in immune reactivity. The rat animal model will be used to examine the phagocytic function of polymorphonuclear neutrophils. Preliminary investigations show higher phagocytic activity in sexually mature female rats, particularly in response to bacterial endotoxin challenge. This finding suggests that sexually mature female rats may have an immunologic advantage over male rats or sexually immature rats. It supports continued study of the immune system of breeding animals, including determination of immune parameters such as superoxide anion measurements and the expression of adhesion molecules in male and female rats who have undergone a traumatic challenge. This research will add to our knowledge of the role of gender and sex hormones in mediating the sequela of septic shock. Award Amount: \$24,876

# ► Title: The Secretary's Conference to Establish a National Action Plan on Breast Cancer

NCI

Understanding how breast cancer develops and how to prevent, diagnose, and treat breast cancer in women across different age groups and different socioeconomic and cultural backgrounds is a priority for the Department of Health and Human Services (HHS). On December 14 and 15, 1993, HHS Secretary Donna Shalala convened the Secretary's Conference to Establish a National Action Plan on Breast Cancer with support from the National Institutes of Health, including the Office of Research on Women's Health. This conference was a first step in response to the presentation of 2.6 million signatures of American citizens to President Clinton in October 1993, requesting a comprehensive strategy to end the breast cancer epidemic. Priorities targeting breast health and breast cancer were identified by conference participants, and the conference proceedings provided an action-oriented framework for the pursuit of breast cancer activities in health care, research, and policy. Award Amount! \$45,000

#### ► Title: Chronic Pain Task Force

NIDR

Under the leadership of the National Institute of Dental Research and in collaboration with the Office of Research on Women's Health and several institutes of the National Institutes of Health, a Chronic Pain Task Force was established to provide support and oversight for a study of the epidemiology and health care costs associated with certain chronic pain conditions. As stipulated by Title XIX, Section 1907, of the National Institutes of Health Revitalization Act of 1993, findings of the study are to be reported to Congress in Fiscal Year 1995. The report will be based on papers covering several chronic pain conditions, including chronic back pain, temporomandibular joint disorders, reflex sympathetic dystrophy syndrome, postherpetic neuralgia, painful diabetic neuropathy, phantom pain, and post-stroke pain. For each condition, experts in epidemiology, health care costs, and chronic pain will address a range of study issues phenomenology, the clinical spectrum, classifications and case definitions, case ascertainment, frequency of condition, health care utilization, direct health care costs and new cost estimates, and research considerations from several perspectives (i.e., basic, clinical, population, health services, and economic). Award Amount \$10,000

## FY 1994 TARGETED RESEARCH PROGRAM

#### Autoimmune Diseases

# ► Title: Chronic Fatigue Syndrome Cooperative Research Center

NIAID

The parent project seeks to elucidate the pathogenesis of chronic fatigue syndrome (CFS) by identifying objective measures that distinguish patients with CFS from healthy individuals and from those with other organic and psychiatric conditions that can produce chronic fatigue. CFS is diagnosed 3 to 4 times more frequently in women than in men and 10 times more often in Caucasians than in other racial populations. This research supplement will be used to conduct a substudy involving Native Americans to investigate potential biological, sociological, and sociocultural reasons for the low prevalence of CFS reported in minority populations. This study will be conducted using a survey research design including questionnaires that have been previously validated in a Native American population. Award Amount: \$49,902

# ► Title: Silicone Polymers: Tissue and Cellular Response

NIAID

This project will analyze silicone polymers in retrieved breast implants and fibrous capsule specimens. The data from this analysis will be correlated with data on the immune response to silicone to examine qualitative and quantitative correlations between silicone polymers released into the tissue and immunological abnormalities. Silicone migration studies will be performed to determine the permeability of the implants. Immunologic evaluation of the study participants will include evaluation of the cellular response, evaluation of silicone antibodies, and measurement of cytokine transcription and translation. This study will add to our knowledge of the potential factors that may impact tissue reactivity to polysiloxanes. Recommendations for the safe use of polymeric biomaterials also will be developed. Award Amount: \$136,679

# ► Title: Program Projects on Autoimmunity

NIAID

The major goals of these program projects include increasing knowledge of etiology and pathogenetic mechanisms involved in autoimmune diseases; generating new information and the expanding of the current knowledge base; and applying this knowledge to develop state-of-the-art technology in basic research that elucidates pathogenic immune mechanisms and shows promise for clinical application in the risk assessment, prevention, early diagnosis, and treatment of autoimmune diseases. Four projects received awards. Award Amount: \$300,000

# STDs/Reproductive Health

# ► Title: Adolescent Health Study

**NICHD** 

This study will identify the attributes of the social and physical environment, family life, school experience, and interpersonal relationships that put adolescents at risk of poor health outcomes and those that help adolescents develop healthy lifestyles. A broad range of data will be collected on adolescent life, health status, and health outcomes, using a nationally representative sample of 7th to 12th grade students and their parents. African Americans and Hispanics will be oversampled. Three interview sessions will be conducted with study participants over a 2-year period. A parallel study of 1,500 youths will be conducted to control for potential biases in the school sample. Award Amount: \$100,000

# ► Title: Pathophysiology of Endometriosis and Leiomyomata Uteri NICHD

The goal of this project is to stimulate new investigations on the mechanisms regulating endometriosis and myoma initiation and growth and to examine biological factors that reduce the incidence of clinical pregnancy in women with endometriosis or leiomyomata uteri. Six projects received funds, including three on endometriosis and three on leiomyomata uteri. The projects on endometriosis are designed to compare the localization, hormonal regulation, and blocking of normal and abnormal metalloproteinases and their tissue inhibitors; to identify the chemotactic factors that enhance migration of macrophages into the peritoneal cavity and promote their activation; and to differentiate patterns of expression of integrins associated with uterine receptivity in women with and women without endometriosis. The projects on leiomyomata uteri will add to our knowledge in major ways by: (1) identifying candidate genes from myomas, characterizing their genetic sequences and investigating their function in the pathogenesis of myomas; (2) examining the effects of steroids on mechanisms of uterine cellular communication by gap junction proteins in myoma and normal myometrial cell cultures; and (3) examining differences in responsiveness to ovarian steroid hormones and other growth regulators between myoma and normal myometrium with respect to extracellular matrix component proteins and autocrine growth factors. Award Amount: \$654,651

# ► Title: Menopause and Health in Aging Women

NIA

This study stimulates comprehensive multidisciplinary research in the natural history of menopause. Seven clinical sites received funds to establish cohorts of 500 premenopausal women for longitudinal studies on the menopausal transition and the effects of this transition on subsequent health and risk factors for age-related disease. Examination of the unique biological and sociocultural factors that may differentially influence the menopausal transition and consequences of menopause in minority women is a priority at each of the clinical sites. Funding was also provided for a coordinating center and central laboratory to facilitate collaboration of the clinical sites and to assist in the collection, management, and analysis of a common dataset. Award Amount: \$573.849

# Urological Health

► Title: Collaborative Research Projects on Urinary Bladder Disorders of Women

NIDDK

This program supports basic and clinical studies focused on the normal and abnormal function of the urinary bladder in women. Representative areas of research include the relationship between interstitial cystitis, recurrent urinary tract infections, and environmental influences; cellular communication in bladder tissues; comparative studies of the molecular biology of bladder development and bladder mucosa, the urethra and the development of bladder disorders; the role of pelvic musculature in bladder function; factors affecting the development of urinary incontinence, and ethnic and racial differences in bladder disorders in women. Fifteen projects received funds. Award Amount. \$500,000

# FY 1994 Administrative Supplements to Ongoing Research Grants

#### Aging

► Title: Aging of Endocrine Cells in Culture
PI: Peter J. Hornsby, Ph.D., Baylor College of Medicine, Houston, TX
Key Words: adrenal gland, gender differences, hormonal regulation

Dehydroepiandrosterone (DHEA), an androgen precursor steroid secreted largely by the adrenal, is a known factor affecting reproductive health and a potential factor affecting susceptibility to diseases that increase with age in women, such as osteoporosis and reproductive organ cancers. This award will support the investigation of the regulation of DHEA and its sulfate (DHEA-S) in adrenocortical cells from women of different ages (range 30 to 60 years) and will compare this regulation with adrenal cells from males of the same age range. Key enzymes critical for the synthesis of DHEA-S will be studied in cell culture under the influence of various hormonal regulators. Differences in enzyme expression will be examined based on age and gender. Award Amount: \$74,000

► Title: Basic Mechanisms of Aging and Age-Related Diseases NIA
PI: Jeanne Y. Wei, M.D., Ph.D., Beth Israel Hospital, Boston, MA
Key Words: cardiovascular response, gender differences, hemodynamic stress

Gender differences may exist in cardiovascular response to acute hemodynamic stress. Distinctions are thought to occur in mechanisms of protein synthesis, ribonucleic acid (RNA) synthesis, and susceptibility to hypoxia/ischemia and adenosinetriphosphatase (ATP) turnover. This project examines gender-related changes in these parameters. Award Amount: \$99,825

► Title: Longitudinal Study—Parents and Children at Age 50

Robert M. Hauser, Ph.D., University of Wisconsin, Madison, WI

Key Words: menopause

PI:

This study will identify educational, familial, and socioeconomic differences among women experiencing menopause. A survey will be conducted to collect data on the type and timing of reproductive organ surgery, use of hormone medications, sources and perceived adequacy of information about the menopause, and use of unconventional treatments or therapies. Data from sister pairs will be used to control for unmeasured sources of heterogeneity in the characteristics of the menopausal experience. Award Amount: \$50,000

Title: Unique Models for the Study of Menopause

NCRR

NIA

NIA

PI: Peter O. Kohler, M.D., Oregon Health Sciences University,

Portland, OR

Key Words: animal model, endocrine, menopause, neural

Menopause, a significant life event in women, is often accompanied by disrupted sleep patterns, inappropriate flushes and sweating, osteoporosis, and enhanced cardiovascular malfunctions. There is a poor understanding of the cause(s), sequence, and relevance of the various menopausal symptoms, and there is little information on the mechanisms by which spontaneous depletion of ovarian estrogen starts the neuroendocrine alterations of menopause. The goals of this project are to characterize endocrine and neural changes as they develop in female perimenopausal rhesus monkeys and to implement creative approaches for selective isolation of ovarian and hypothalamic components that contribute to the "menopausal syndrome." After identifying and measuring key endocrine/neural parameters, possible key factors will be replaced selectively in X-irradiated and/or desipramine-treated females to evaluate their individual efficacies. Award Amount: \$100,000

Title: Reproductive Aging and the Human Hypothalamus

PI: Naomi E. Rance, M.D., Ph.D., University of Arizona Health

Sciences Center, Phoenix, AZ

Key Words: hypothalamus, luteinizing-releasing hormone, postmenopausal,

tachykinins

Dramatic changes, including hypertrophy of neurons in the hypothalamic reproductive control center, have been found in the brains of postmenopausal women. The neurons have an important role in regulating estrogen receptors, tachykinins, and luteinizing-releasing hormone (LRH). Plasma luteinizing hormone is markedly increased in postmenopausal women; however, the cause is not known. This award will support examination of neurons containing LRH to determine if hypothalamic LRH gene expression is increased in postmenopausal women. Secondarily, the investigator will attempt to demonstrate an anatomic link between tachykinin and LRH neurons by evaluating the presence of messenger RNA for tachykinin receptors in hypothalamic reproduction control center neurons. Results of the project will increase understanding of the regulation of human reproduction, postmenopausal changes in the hypothalamic reproductive control center, and possible relationships between tachykinins and flushes. Award Amount: \$99,852

► Title: Aromatase in Adipose: Relationship to Aging and Cancer NIA

PI: Evan R. Simpson, Ph.D., University of Texas Southwestern

Medical Center at Dallas, Dallas, TX

Key Words: adipose tissue, aromatase expression, estrogen biosynthesis

Estrogen formation in adipose tissue is an important factor in several diseases affecting women, including breast cancer, endometrial cancer, and osteoporosis. Cellularity and cell composition are believed to be important factors in controlling the expression of aromatase in adipose tissue. This project studies the cellularity of adipose tissue to determine the basis for age-

dependent increases in the expression of adipose aromatase in women of advancing age. The results of this project will contribute to the understanding of the pathophysiology of diseases in women associated with estrogen biosynthesis in adipose tissue. The investigation includes examining the mechanisms underlying adipose stromal cell differentiation and the subsequent loss of aromatase expression. Award Amount: \$50,000

## Alcohol Abuse/Alcoholism

Title: Alcohol Effects in Postmenopausal Women

NIAAA

NIAAA

PI:

Judith S. Gavaler, Ph.D., Oklahoma Medical Research Foundation,

Oklahoma City, OK

Key Words: estrogens, postmenopausal, recruitment, Native American

This project examines the effects of moderate alcoholic beverage use and alcohol abuse on estrogen levels in a group of minority and Native American postmenopausal women. This award will allow for differences in alcohol use and abuse to be explored between the various ethnic groups included in the study. In addition, a new approach to recruitment and enrollment of Native American women will be piloted. Award Amount. \$50,000

► Title: Probabilities of Drunken Driving Among DUIs and

U.S. Public Law NIAAA

PI:

PI:

Mervyn W. Perrine, Ph.D., Vermont Alcohol Research Center.

Colchester, VT

Key Words: driving, lesbians

Available data suggest that drinking and alcohol-related problems among lesbians are more prevalent than in the general female population and that heavy drinking continues across the life span, increasing the risk of alcohol-related problems and the likelihood of drunk driving. The goal of the award is to identify drinking and driving patterns among lesbians, differentiate possible categories of female drinking drivers, and the reasons for drinking among the lesbian driving population. Relationships among patterns of alcohol consumption, loss of controlled drinking, and drunk driving among lesbians will be studied. Award Amount: \$67,986

► Title: Psychopharmacologic Treatment of Alcoholism

Jan A. Fawcett, M.D., Rush-Presbyterian-St. Luke's Medical Center,

Chicago, IL

Key Words: buspirone, gender differences, lithium carbonate

This study tests the efficacy of lithium carbonate and buspirone for the treatment of alcoholism. Sociodemographic variables that may predict favorable drug responses in the two treatment conditions will be examined. A sample of women will be enrolled in the buspirone arm of an ongoing study to permit an examination of gender differences. Award Amount: \$48,636

► Title: Alcohol, Psychosocial Factors, and Adolescent Development NIAAA
PI: Paul E. Baer, Ph.D., Baylor College of Medicine, Houston, TX

Key Words: ethnicity, gender differences, psychosocial, adolescents

This study is based on a grant to study a developmental model of adolescent substance abuse that incorporates psychosocial interaction models and the roles of ethnicity and individuation. This award will examine gender differences in problem behavior and the role of problem behavior in the development of alcohol and other drug use. It will also address the specialized effects of acculturation as they are involved in substance abuse among girls. Award Amount: \$50,000

#### Behavioral Studies

► Title: Adolescents with Handicaps: Life Span and Cultural Concerns NICHD

PI: Janet B. Blacher, Ph.D., University of California, Riverside, CA

Key Words: coping, mental retardation, stress, Hispanic, adolescents

Little is known about how women cope with an adolescent who has severe handicaps. An ongoing study of adoptive and birth families with severely retarded adolescent children includes Hispanic women and their children. The psychological and physical effects of stress on mothers who cope with very retarded offspring will be studied. This award supports the inclusion of a comparison group of low-income Hispanic mothers without disabled children. Data will be collected to determine differences between Hispanic women coping with a child's disability and other Hispanic mothers. Award Amount: \$49,885

► Title: Psycholinguistic and Biological Mechanisms in Dyslexia NICHD

PI: Bennett A. Shaywitz, M.D., Yale University, New Haven, CT

Key Words: cognitive status, estrogen, postmenopausal

The study explores hormonal influences on the development of reading and reading disability among female subjects. The study sample will be expanded to include postmenopausal women and directly address questions concerning the influence of estrogen on cognitive status. Award Amount: \$100,000

► Title: Adaptation After Stroke: Patient and Support Person NINR

PI: Rosemarie B. King, Ph.D., Rehabilitation Institute

Research Corporation, Chicago, IL

Key Words: gender differences, health maintenance, psychosocial

adaptation, retention, stroke, minority

The purposes of the study are to describe the process of adaptation of patients with stroke and their primary support persons and to assess the relationship between selected variables and psychosocial adaptation. The objectives of the study will focus on: (1) retaining minority female primary support persons and patients in the longitudinal parent study; (2) examining gender differences in health maintenance activities, physical health, depression, and coping, using qualitative and quantitative methods; and (3) examining the relationship between depression and health outcomes among female primary support persons. Award Amount: \$28,484

► Title: Smoking Cessation, Weight Gain, and Exercise in

Underserved Women

NCI

PI: Bess H. Marcus, Ph.D., The Miriam Hospital, Providence, RI

Key Words: low literacy, recruitment, smoking cessation, minority

This award will support the design of recruitment and intervention strategies for a low-literacy population to increase participation of underserved women in a smoking cessation program. Innovative techniques for retention will be identified, including conducting a series of focus groups to examine barriers affecting participation of underserved minority women in smoking cessation programs. Changes in body weight and exercise levels will be evaluated. Award Amount: \$99,287

► Title: Chronically Disabled Adults: Mental Health of Caregivers NIMH

PI: Rachel A. Pruchno, Ph.D., Menorah Park Center for the Aging,

Bethesda, OH

Key Words: caregivers, disabilities, mental health, recruitment, African American

This project examines the effects of chronic disabilities of adult children on the mental health of their aging mothers. Design of the project is based on a conceptual framework that posits

the mother's mental health is a function of: (1) the adaptive functioning of her child, (2) the resources available to her (e.g., physical health, financial resources, and social environment), and (3) the quality of the mother-child relationship. This award will increase recruitment of African-American women and modify the conceptual framework to include race as a moderating factor. Award Amount: \$50,000

Title: Locomotor Activity Rhythms in Psychiatric Illness NIMH
PI: Martin H. Teicher, M.D., Ph.D., McLean Hospital, Belmont, MA
Key Words: attention-deficit hyperactivity disorder, gender differences

Attention-deficit hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders of childhood. Boys are five to nine times more likely to receive treatment than girls, though community assessment surveys suggest that differences in prevalence are relatively minor. Girls, however, have been excluded from many key studies of ADHD. The study will test the hypothesis that there are only minor gender differences in the prevalence of hyperactivity and inattention between boys and girls and that teachers are more likely to detect these problems in boys but frequently fail to detect them in girls. The award will support development of criteria for detecting hyperactivity and design of an appropriate instrument. Award Amount; FY 94 \$50,000; FY 95 \$50,000

## Cancer

Title: Treatment Barriers of Women with Breast Abnormalities NCI
PI: Ramon Velez, M.D., Reynolds Health Center, Winston-Salem, NC
Key Words: barriers, compliance, low literacy, minority

Few studies have investigated the negative psychosocial consequences of abnormal screening results, which may result in failure to comply with treatment and future screening tests. The purposes of the project are to explore participant noncompliance with recommended follow-up and to identify barriers to treatment among low-income minority women with breast abnormalities. Specific aims of the research are to: (1) identify behavioral, cultural, and system barriers related to compliance with treatment recommendations following an abnormal mammogram; (2) develop a low-literacy brochure that addresses these barriers; and (3) test the effect of the brochure in improving compliance with treatment recommendations in a randomized trial. Interventions resulting from this study may help primary care physicians and mammography screening facilities improve compliance of low-income minority women with mammography screening, follow-up, and treatment. Award Amount: \$49,076

► Title: Low-Literacy Informed Consent for Breast Cancer Patients NCI
Pl: Douglass C. Tormey, M.D., Ph.D., Eastern Cooperative Oncology
Group, Denver, CO

Key Words: compliance, informed consent, low literacy, recruitment

Informed consent statements are often complex and are frequently cited as a barrier to accrual of under-represented populations in clinical trials. The purpose of the project is to evaluate the potential impact of a low-literacy informed consent statement on the accrual and the compliance of minority women participating in the intergroup study for women with either node-negative or one to three node-positive breast cancer. The low-literacy informed consent statement will be developed and pilot tested at a Minority Community Clinical Oncology Program member site. Results from the pilot test will be used to design a randomized comparison between the low-literacy informed consent statement and standard informed consent in a clinical trial setting. Award Amount: \$36,869

► Title: Post-Traumatic Stress Disorder in Life Threatening Illness—

Phenomenology and Risk NIMH

PI: Bonnie L. Green, Ph.D., Georgetown University, Washington, DC Key Words: breast cancer, post-traumatic stress disorder, African American

The project examines whether post-traumatic stress disorder occurs in women diagnosed with early-stage breast cancer and if the risk for this diagnosis is increased in women with a history of trauma. The study will be expanded to include the recruitment of Caucasian and African-American women and women with more advanced disease. The psychological impact of early- versus late-stage disease and differences in adaptation between Caucasian and African-American women will be explored. Award Amount: \$46,373

► Title: Estrogen and Progesterone Expression in Lung Cancers NCI

PI: Eliot R. Spindel, M.D., Ph.D., ORPRC/Medical Research Foundation

of Oregon, Beaverton, OR

Key Words: biological markers, gastrin-releasing peptide, hormonal receptors

Gastrin-releasing peptide (GRP) stimulates the growth of some small cell lung carcinomas. Estrogen stimulates GRP expression in the cervix and correlates strongly with the presence of estrogen and progesterone receptors in breast cancer. There are no published data on the differences in hormonal expression in lung cancer in women versus men or how estrogen and progesterone affect the prognosis of small cell lung carcinoma in women. This award will explore whether GRP expression in lung cancer is modulated by estrogen and progesterone receptors. Specifically, estrogen, progesterone, and GRP expression will be characterized in small cell lung carcinoma and large cell lung carcinoma using archival specimens and small cell lung carcinoma cell lines. Correlations between data obtained from archival specimens and clinical outcome will be evaluated. Award Amount: \$99,958

► Title: Nutritional Biochemistry and Neoplasia in Oral Tissues NIDR

PI: John P. Richie, Jr., Ph.D., American Health Foundation,

Valhalla, NY

Key Words: lung cancer, oral cancer, metabolism, NNK, smoking

Several studies suggest that female smokers are at greater risk than male smokers for being diagnosed with lung cancer and other tobacco-related cancers. The difference in relative risk may result from a lower capacity in women to detoxify the tobacco-specific carcinogen NNK, the likely causative agent for both lung and oral cancers in humans. The award will test the hypothesis that women are at greater risk for lung as well as oral cancers due to differences in metabolism of the NNK. Metabolic capacity for detoxification of NNK and its metabolites will be compared in male and female smokers. A second study using a large database on smoking and cancer will examine whether or not women smokers are at greater risk for oral cancer than men who smoke an equivalent number of cigarettes. Award Amount: \$49,926

► Title: Pheromones, Behavior, and the Regulation of Fertility NIMH

PI: Martha K. McClintock, Ph.D., University of Chicago, Chicago, IL

Key Words: animal model, breast cancer, menstrual cycle

Socially isolated female rats have a higher incidence of spontaneous mammary tumors than female rats living in groups with other females. The factor mediating this relationship is hypothesized to be key components of the ovarian-cycle history. This study investigates the behavioral and social regulation of fertility and menstrual cycles by testing two alternative mechanisms by which social isolation increases risk for mammary cancer among rats. Award Amount: FY 94 \$49,690; FY 95 \$49,401

► Title: Monkey Models and Women's Health NCRR

PI: Thomas B. Clarkson, D.V.M., Bowman Gray School of Medicine of

Wake Forest University, Winston-Salem, NC

Key Words: animal model, hormones, preneoplastic lesions

The project will use molecular models for detection of preneoplastic lesions to evaluate hyperplasia/dysplasia in the breast and uterus of monkeys being subjected to various hormonal manipulations. Mammary and reproductive tissues collected for this study represent a unique resource for assessing proliferative lesions induced by hormonal therapies. Among the treatments to be studied will be premenopausal influences of contraceptive steroids and postmenopausal influences of hormone replacement. Award Amount. \$99,999

## Cardiovascular Disease

Title: Sex Hormones Modulate Vascular Adrenoceptors in Women
 PI: Robert R. Freedman, Ph.D., Wayne State University, Detroit, MI
 Key Words: catecholamines, estradiol, progesterone, vascular responses

Considerable evidence exists that sex hormones modulate vascular responses and that they may be a mechanism for the gender difference in peripheral vascular adrenoceptors. The award will test the effects of 17 beta-estradiol and progesterone on alpha-1, alpha-2, and beta-adrenergic responses in normally menstruating women. Subjects pretreated with exogenous estradiol, progesterone, or placebo will participate in three separate experiments, including: (1) intraarterial infusions of phenylephrine, clonidine, or isoproterenol; (2) measures to illicit the cold reflex; and (3) tests for reactive hyperemia. Plasma estradiol, progesterone, and catecholamine levels will be measured during each experiment. Award Amount. \$49.921

Title: Estrogen and Vascular Function in Postmenopausal Women NHLBI
PI: Peter Libby, M.D., Brigham and Women's Hospital, Boston, MA
Key Words: hormone replacement therapy, postmenopausal, vascular function

This project examines the role of cells in blood vessel walls relative to thrombosis, interactions with leukocytes, vascular tone, and the growth and metabolism of neighboring cells. Data from this project will guide the development of clinical strategies for improved management of vascular patients. This award will support examination of the effects of estrogen replacement therapy in postmenopausal women on vascular function of the peripheral, coronary, and pulmonary circulations. Award Amount. \$99,960

Title: Epidemiology of Lead, Diet, and Blood Pressure
 Pl: Howard Hu, M.D., Brigham and Women's Hospital, Boston, MA
 Key Words: blood pressure, diet, lead exposure

To understand target organ damage in women with diseases such as osteoporosis, it is important to evaluate bone lead stores. The project studies the effects of low-level lead exposure on blood pressure in women. Diet and other related factors will be explored. Award Amount: \$50,000

► Title: Epidemiology of Carotid Artery Disease in Older Adults NHLBI

PI: Kim S. Tyrrell, Ph.D., University of Pittsburgh, Pittsburgh, PA Key Words: atherosclerosis, carotid ultrasound, hormone replacement therapy,

African American

Measures of carotid atherosclerosis have been found to predict cardiovascular morbidity and mortality. Individuals at high risk for development of cardiovascular disease may be identified early through procedures such as carotid ultrasound. Once individuals are identified, aggressive risk-factor modification can be implemented. This award will evaluate differences in carotid atherosclerosis across three groups of African-American women: (1) those with hysterectomy, (2) those with hysterectomy and bilateral oophorectomy, and (3) normal controls. The effectiveness of hormone replacement therapy and its relationship to atherosclerosis will be evaluated by measurements of ultrasound in the carotid arteries. Award Amount: \$50,000

# Depression

► Title: Behavioral Factors in Coronary Heart Disease NHLBI

PI: Redford B. Williams, M.D., Duke University, Durham, NC Key Words: coronary heart disease, depression, gender differences

The project examines the role of biobehavioral factors in the etiology, pathogenesis, and course of coronary heart disease (CHD). Preliminary data suggest that depression is a risk factor for CHD incidence and mortality independent of pre-existing disease; however, most of the research has been conducted on men. Depression is particularly prevalent in women, yet few studies document the association of depression to CHD and risk-factor endpoints in women. This award will examine the impact of depression on CHD risk factors and clinical endpoints in women. Award Amount: \$49,971

► Title: Drug Treatment of Depression in Nursing Home Aged NIMH

PI: Ira R. Katz, M.D., Ph.D., University of Pennsylvania,

Philadelphia, PA

Key Words: postmenopausal, sex steroids, nursing home residents

The purpose of the study is to evaluate the pharmacological treatment of depression in elderly nursing home residents. The relationship between plasma levels of endogenous sex steroids and depression in postmenopausal women will be compared to the relationship between steroid level and antidepressant drug responses in frail elderly women. Award Amount: FY 94 \$49,876; FY 95 \$49,876

► Title: Relapse and Recurrence in Geriatric Psychotic Depression NIMH

PI: Barnett S. Meyers, M.D., New York Hospital-Cornell Medical

Center, New York, NY

Key Words: cognitive status, elderly, electroconvulsive therapy, estrogen

The study longitudinally follows a group of depressed women at high risk for relapse to determine whether: (1) estrogen influences the course of depression, (2) estrogen influences pharmacokinetic factors in depressed geriatric women under treatment, and (3) estrogen supplement affects cognitive status in older women who have undergone electroconvulsive therapy, a therapy with known cognitive effects. Award Amount: FY 94 \$40,000; FY 95 \$40,000

# Developmental/Reproductive Biology

► Title: Metalloproteinases and Mammary Gland Remodeling NCI

Pl: Zena Werb, Ph.D., University of California, San Francisco, CA

Key Words: animal model, mammary gland maturation

In the mammary gland, interaction between matrix and epithelium regulates gene expression during pregnancy, lactation, and involution. The loss of extracellular matrix may be the key factor in the loss of differentiated function at weaning. Due to a lack of acceptable biological models for testing, little information is available about the process of mammary gland maturation. The SL-1-transgenic mouse models developed through this project will be used to explore the biological effect of the loss of proteinases and inhibitors in mammary gland maturation. This research will address fundamental concepts in cell biology with implications for developmental biology, reproductive biology, and cancer biology. Award Amount: \$100,000

Title. Resource Center for Complex Carbohydrates NCRR

Pl: Peter Albersheim, Ph.D., University of Georgia, Athens, GA

Key Words: egg receptors, fertilization, sperm binding

The project will use newly refined analytical techniques developed by the NIH Resource Center for Biomedical Complex Carbohydrates at the University of Georgia to deduce the precise chemical structure of the oligosaccharide that serves as a specific receptor for sperm binding. Identification of the receptor could contribute to the development of a new type of contraceptive. This research is being conducted in collaboration with investigators from the M.D. Anderson Cancer Center who have pioneered studies on sperm-binding proteins and egg receptors. Award Amount. \$49,997.

► Title: Bio-Organic Biomedical Mass Spectrometry Resource NCRR

PI: Alma L. Burlingame, Ph.D., University of California at

San Francisco, San Francisco, CA

Key Words: cytotrophoblasts, mass spectrometry, pre-eclampsia

In normal pregnancy, fetal cytotrophoblasts invade maternal (uterine) arterioles, thus bringing oxygenated blood to the placenta. In pre-eclampsia, cytotrophoblast invasion is abnormally shallow and the cells become hypoxic. Current data suggest that the maternal syndrome (proteinuria, malignant hypertension) is caused by toxic factors released by hypoxic cytotrophoblasts. Using two-dimensional gel analysis, the investigator has shown that culturing cytotrophoblasts under hypoxic conditions results in upregulated production of seven discrete proteins. The study will use mass spectrometry to determine the structure of these proteins. Knowing their structure is the first step in assessing the involvement of the proteins in the etiology of pre-eclampsia. Award Amount: \$100,000

► Title: Therapies for Recurrent Miscarriage—A Randomized Study
PI: Carole Ober, Ph.D., University of Chicago, Chicago, IL
Key Words: human leukocyte antigen, immunotherapy, miscarriages

Through a randomized clinical trial, the efficacy and safety of two therapeutic approaches for preventing repeated miscarriages will be compared, including immunotherapy using paternal leukocytes combined with prenatal supportive care versus prenatal supportive care alone. The purpose of this award is to examine the role of human leukocyte antigen *G* (HLA-*G*) genotypes in women with recurrent spontaneous abortions. The data will be used to determine whether there is a preferential loss of HLA-*G* compatible fetuses in couples with recurrent spontaneous abortions who were immunized with saline and whether immunotherapy preferentially "rescues" HLA-*G* compatible fetuses in couples immunized with the father's cells. Award Amount: \$97,012

**NICHD** 

**NIDA** 

► Title: Risk Factors Associated with Uterine Fibroid Growth

PI: Kristen H. Kjerulff, Ph.D., University of Maryland,

Baltimore, MD

Key Words: hysterectomy, leiomyomata

The study examines potential risk factors for uterine fibroids, such as smoking, obstetrical and gynecological history, exercise, and obesity, by comparing 500 women undergoing hysterectomy for pathologically confirmed fibroids with 500 controls matched by age, race, and physician. This award will support the recruitment of 100 women with fibroids who have not undergone hysterectomy for inclusion in the primary study. The objective is to determine the extent to which risk factors differ between women who have not had a hysterectomy and women who have undergone the procedure. Relationships with other factors will be investigated, including education, income, insurance coverage, completion of childbearing, and physician practice style. Award Amount: \$49,656

# Drug Abuse

► Title: Cocaine/Ethylcocaine Metabolism and Behavioral Studies NIDA

Pl: William F. Bosron, Ph.D., Indiana University School of

Medicine, Indianapolis, IN

Key Words: alcohol and cocaine co-abuse, animal model, gender differences,

metabolism

The study will determine gender differences in the distribution of key cocaine metabolites after coadministration of alcohol and cocaine. Tissue distribution of cocaine esterases and ethyl ester transferases will be evaluated. The outcome of this study will bridge gaps in current knowledge of gender-specific differences in the pattern of cocaine and alcohol co-abuse and cocaine metabolism in women. Award Amount: \$50,000

► Title: A High-Risk Prospective Study of Drug Use and Crime:

Gender Differences

PI: Margaret E. Ensminger, Ph.D., Johns Hopkins University,

Baltimore, MD

Key Words: behavior, adolescent, African American

The study examines the developmental epidemiological factors contributing to drug use and other problem outcomes. The study sample includes a cohort of African-American adults who have been followed longitudinally since the first grade. The research identifies early developmental patterns leading to successful and unsuccessful role performance and psychological status. The outcomes of the study are to: (1) examine the role of individual and environmental factors measured in childhood and adolescence that presage drug use and other problem outcomes, (2) examine consequences of adolescent substance use and other problem behaviors on adult role performance and psychological well-being, and (3) identify the pathways to achievement and successful outcomes. Award Amount: \$98,061

► Title: Drug Effects on Behavior: Workplace Implications NIDA

PI: Marian Fischman, Ph.D., New York State Psychiatric Institute,

New York, NY

Key Words: alprazolam, menstrual cycle, workplace performance

A substantial number of women have significant premenstrual mood changes that can impact performance in the workplace. The study will assess the effects of alprazolam on psychomotor performance across phases of the menstrual cycle in women with significant premenstrual symptoms. The effects of alprazolam on performance during both the late luteal and follicular phases of the menstrual cycle will be evaluated to examine the interactions of drugs with abuse liability and behaviors relevant to workplace productivity and

safety. The results of this study might be used to develop an approach to screen medications for their potential to impair symptoms and impact performance in the workplace and for their abuse liability. Award Amount: \$49,984

► Title: Evaluating a Desipramine Ceiling in Cocaine Abuse Treatment NIDA

PI: Frank H. Gawin, M.D., UCLA Drug Abuse Research Center,

Los Angeles, CA

Key Words: antidepressant therapy, crack cocaine, desipramine,

gender differences, recruitment

This project evaluates the effectiveness of the antidepressant desipramine on promoting abstinence in cocaine and other stimulant abusers. Experience has shown that women respond differently than men to most psychotropic drugs, including antidepressants. It is essential, therefore, to compare the safety and efficacy of potential medications in both men and women addicts. This award will increase the proportion of women included in the primary study by 50 percent. This will be accomplished by using three innovative methods of recruitment. Support of this effort will enhance the statistical evaluation of gender differences in the efficacy and safety of desipramine and potential gender differences in a reported ceiling effect of desipramine dosage. Study results will provide invaluable missing information about various aspects of gender differences in stimulant addiction and its treatment. Award Amount: \$50.000

Title: Center for Therapeutic Community Evaluation Research NIDA

PI: George DeLeon, Ph.D., National Development and Research

Institutes, New York, NY

Key Words: therapeutic community, treatment relapse, adolescent

The project will support post-treatment follow-up interviews of female adolescents who have been in residential therapeutic communities for treatment of substance abuse problems and accompanying disorders. The purposes of the interviews are to: (1) identify the risk and protective factors associated with post-treatment relapse and retention among female adolescents who have been in therapeutic communities, and (2) investigate the interaction of race/ethnicity, family instability, relapse, and retention. Award Amount: \$50,000

## Endocrine Disorders

► Title: Mild Hyperparathyroidism—A Randomized Trial of Surgery
PI: D. Sudhaker Rao, M.D., Henry Ford Hospital, Detroit, MI

Key Words: lipid abnormalities, parathyroidectomy, primary hyperparathyroidism

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder that can lead to long-term devastating consequences for mineral metabolism, thereby adversely affecting bone quality and increasing the risk of fracture. Other complications include renal and cardiovascular effects. Considerable controversy exists regarding the potential risks and benefits of surgery versus medical management of PHPT. The trial will recruit and study a group of patients with mild PHPT and randomize them to surgery or no surgery. This award will support examination of the increased risk of cardiovascular morbidity and mortality in patients with PHPT compared to age- and sex-matched controls. The substudy objectives include: (1) determining the potential lipid abnormalities in patients with mild PHPT and the effect(s) of parathyroidectomy (PTX) on these parameters, and (2) determining the effect of mild PHPT on iliac bone histomorphometry and assessing the effects of PTX on this parameter. Award Amount: \$87,268

► Title: Relation of Thyroid Function and Disease to the Menstrual Cycle NCRR

PI: Robert M. Carey, M.D., University of Virginia, Charlottesville, VA Key Words: genetics, menstrual cycle, thyroid disease, thyroid hormone secretion,

autoimmune disease

Thyroid disease is four times more common in women than in men. The clinical study aims to examine the relationship of thyroid hormone secretion to the menstrual cycle and to identify factors that might contribute to variations in thyroid function and thyroid disease. Previous laboratory research by the investigator demonstrates a genetic basis for variation in thyroglobin structure. The award will support the use of laboratory methods to examine a wide range of thyroid diseases of women, particularly autoimmune thyroid disease, simple and multinodular goiter, and thyroid cancer. The results of the clinical and laboratory studies will expand knowledge of the factors that influence thyroid function and contribute to the development of thyroid disease in women. Award Amount: \$96,614

## Genetics

► Title: National Flow Cytometry and Sorting Research Resource NCRR

National Laboratory

PI: James H. Jett, Ph.D., University of California, Los Alamos

National Laboratory, Los Alamos, NM

Key Words: flow cytometry, pregnancy, prenatal genetic screening

The study will use advanced flow cytometry methods, being developed under the primary grant, to develop a new method of obtaining fetal cells for prenatal genetic screening. The process involves the detection and isolation of fetal cells from maternal peripheral blood. The detection method will rely upon: (1) the presence of steroid enzymes in trophoblast cells, as measured in single-cell, enzyme-specific assays using advanced flow cytometry for high-speed, multiparametric, rare-event sorting; and (2) biochemical probe systems developed previously within the National Flow Cytometry Resource. This approach for detecting fetal cells in maternal blood will be applied to the development of a noninvasive test for prenatal genetic screening in early pregnancy. Award Amount: \$100,000

# Genitourinary/Urologic Disease

► Title: Epidemiology of Incontinence in African-American Women NIDDK

PI: Anna R. Herzog, Ph.D., University of Michigan, Ann Arbor, MI

Key Words: epidemiology, urinary incontinence, African American

Urinary incontinence affects thousands of women of all ages. The study will survey 1,800 persons age 40 and older. The objectives of the study are to: (1) establish national prevalence and incidence rates of urinary incontinence among older adults, (2) confirm specific symptoms as risk factors for urinary incontinence, and (3) evaluate various questionnaire formats. Previous studies suggest that African-American women are at a two times greater risk for urinary incontinence than Caucasian women and that this incontinence occurs at an earlier age. To address this further, the award will be used to recruit African-American and middle-aged women in the epidemiological survey. The survey will use a previously validated telephone sampling questionnaire. Award Amount: \$49,500

Title: Recruitment of African-American Females into AASK Study NIDDK

PI-Julia A. Brever, M.D., Vanderbilt University, Nashville TN Key Words: AASK study, drug therapy, hypertension, kidney disease,

recruitment. African American

End-stage renal disease disproportionately affects African Americans in the United States. Vanderbilt University and Meharry Medical College are consortium clinical centers for a multicenter, randomized clinical trial, the African-American Study of Kidney Disease and Hypertension (AASK). This trial tests whether two levels of blood pressure control and three different classes of antihypertensive drugs (calcium channel blocker, beta-blocker, and angiotensin converting enzyme inhibitor as primary therapy) are able to reduce significantly the rate of kidney function loss. The award will improve the recruitment of African-American women into the full-scale phase of AASK by (1) soliciting assistance from the female African-American community, state leaders, female African-American physicians (especially obstetricians, gynecologists, and pediatricians), female African-American teachers. and corporations and businesses who employ a large percentage of female African Americans: and (2) targeting churches, African-American civic organizations, sororities, beauty shops, grocery stores, and pharmacies in African-American neighborhoods. Award Amount. \$81,052

Title: Enhancing Recruitment of Women in the Full-Scale AASK Trial NIDDK

PI: W. Dallas Hall, M.D., Emory University, Atlanta, GA AASK study, hypertension, drug therapy, kidney disease, Key Words:

recruitment. African American

The award will enhance the recruitment of African-American women into the African-American Study of Kidney Disease and Hypertension (AASK) by implementing church-based recruitment, targeting beauty salons for screening for hypertension, and enlisting the aid of African-American women's organizations to publicize the study Award Amount, \$48,493

#### Hormonal Disorders

Hormonal Control of Adapose Gene Expression **NIDDK** Title:

PI-M. Daniel Lane, Ph.D., Johns Hopkins University,

Baltimore, MD

Key Words: cortisol, hormones, metabolism, molecular genetics, obesity

The goal of this award is to determine the underlying mechanism by which elevated cortisol levels contribute to central (abdominal) obesity in women. The investigators will test the hypothesis that glucocorticoid and estrogen, acting through one or more genetic transcription factors, is responsible for this phenomenon. Studies conducted in male and female mice will investigate the role of hormones on gene expression and adipose cell development. This work is expected to elucidate basic cellular mechanisms of adipose cell metabolism. Award Amount: \$100.000

#### Immunology

Title: T-Cells in the Induction of Lupus NIAMS

Bruce C. Richardson, University of Michigan, Ann Arbor, MI Key Words: autoimmune disease, genetics, lupus, two-dimensional gel analysis

Research shows that treatment of lymphocytes in vitro with hypomethylating agents results in the development of self-reactivity. Further, cells treated with hypomethylating agents are able to induce lupus-like disease when administered to normal mice. This study will examine the genes and effector mechanisms that are important in this form of drug-induced lupus. The technique of two-dimensional DNA gel analysis of genomic DNA fragments will be used to locate the specific genes and regions affected by hypomethylating agents. Observations in experimental systems will be applied to human lupus cells and may yield new insights into the genetics of the disease. Award Amount: \$100,000

► Title: Alcohol, Infection, and Host Response NIAAA

PI: John J. Spitzer, M.D., Louisiana State University Medical Center,

New Orleans, LA

Key Words: alcohol, animal models, autoimmune disease, immune function

Little information is available on gender differences in the negative effects of alcohol abuse on the immune system or the role of alcohol on the development of autoimmune disease. The study will test the hypothesis that host defense mechanisms involving liver macrophages and neutrophils in female rats will be different from those expressed in male rats. Studies to investigate cell types and functions will be conducted with female rats in various stages of estrous cycle and various time points in the life span. Award Amount: \$50,000

► Title: Sjögren's Xerostomia: Viral/Immunological Etiology NIDR

PI: William R. Gallaher, Ph.D., Louisiana State University

Medical Center, New Orleans, LA

Key Words: autoimmune disease, Sjögren's syndrome, xerostomia, Hispanic

Sjögren's syndrome (SS) has a multifactorial etiology, involving genetic, viral, hormonal and psychoneuroimmunological mechanisms. The study will provide a multidisciplinary integrated approach to the study of the etiology and oral sequelae of SS. The study will be expanded to recruit Mexican-American women with SS and to examine the characteristics of this autoimmune disease in a Mexican-American population. Award Amount: \$100,000

Title: Mechanisms and Pathogenesis of Primary Biliary Cirrhosis
 PI: Merrill E. Gershwin, M.D., University of California, Davis, CA
 Key Words: autoimmune disease, molecular mechanisms, primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is an uncommon autoimmune hepatic disorder found predominantly in women. PBC is characterized by the immune-mediated destruction of bile ducts, and accounts for 30 to 40 percent of all adult liver transplants in the United States. The purposes of the study are to elucidate the nature of the T-cell mediated response and to determine why immune damage is confined to the biliary epithelium despite the widespread distribution of the target autoantigens. Immunofluorescence and immunochemical techniques will be used to investigate questions about autoantigen production. Potential results from the study will further the understanding of this condition and may lead to protocols for the treatment of PBC. Award Amount: \$100,000

# Infectious Disease

► Title: Adolescent Alcohol Use and High-Rish Sexual Behavior NIAAA

PI: Lynne M. Cooper, Ph.D., State University of New York,

Buffalo, NY

Key Words: sexual behavior, adolescents

This study examines the relationship between alcohol use and sexual behavior and the associated risks for development of sexually transmitted diseases and human immunodeficiency virus in adolescents. Data will be collected on the male partners of young women currently enrolled in the study. Partner and relationship characteristics are hypothesized to be important in understanding the choices regarding risky versus nonrisky behaviors. Award Amount: \$100,000

► Title: Herpes Simplex, Pregnancy, Neonatal Risk, and Flost Defense NIAID

PI: Charles G. Prober, M.D., Stanford University School of Medicine.

Stanford, CA

Key Words: neonatal herpes infection, adolescent, minority

Neonatal herpes infections occur in infants exposed to reactivated and primary maternal infection. Prevention of neonatal herpes depends upon identifying seronegative women in discordant couples as well as seropositive women at risk for reinfection. The project will conduct seroepidemiological studies in a nonpregnant adolescent population, with particular emphasis on racial differences in the epidemiology of herpes simplex. The study design will incorporate microbiological and behavioral outcomes. The cohort will include approximately 2,000 "at-risk" adolescents from juvenile detention centers, school-based clinics, community youth clinics, and youth/adolescent clinics. Award Amount: \$49,970

Title: Pain in the Ambulatory AIDS Patient NIMH

PI: William Breitbart, M.D., Sloan-Kettering Institute for

Cancer Research, New York, NY

Key Words: AIDS, gender differences, pain, psychosocial

The goal of the project is to study the impact of pain on quality of life and psychosocial adjustment in a sample of ambulatory AIDS patients. The award will be used to expand enrollment of women to. (1) identify and classify pain syndromes in women with AIDS; (2) characterize AIDS-related pain and pain treatment in terms of intensity, frequency, and treatment efficacy; (3) assess the relationship between psychosocial functioning and quality of life variables; (4) describe the natural history of pain and its sequelae over time; and (5) examine the influence of gender and gender-demographic interactions on pain experience and their impact on quality of life and psychosocial adjustment. Award Amount: \$50,000

► Title: CAPS: Adherence to TB and HIV Early Intervention

in Homeless Adults

NIMH

PI: Thomas J. Coates, Ph.D., University of California at

San Francisco, San Francisco, CA

Key Words: coping skills, HIV, homeless, psychosocial, African American

The study pilots an intervention to reduce high-risk behaviors in homeless and unstably housed women. The intervention will include trained female peer health advisors as facilitators to teach coping skills and develop health-promoting social networks. Three outcomes will be measured: (1) use of medical services for screening and treatment of human immunodeficiency virus, tuberculosis, sexually transmitted diseases, and violence reduction; (2) change in frequency of behaviors that put homeless women at high risk for the target infections and violence; and (3) change in coping skills and social supports assessed by self-report and clinical evaluation. Award Amount. FY 94 \$49,985; FY 95 \$50,000

► Title: HIV Inhibitory Factors in Human Saliva NIDR

PI: Daniel Malamud, Ph.D., University of Pennsylvania, Philadelphia, PA

Key Words: AIDS, breastfeeding, HIV transmission

The project is designed to identify and characterize factors present in human saliva that decrease HIV infectivity. The award will be used to increase the number of HIV-seropositive female participants enrolled in the study and to explore the potential role of saliva, if any, in HIV transmission during breastfeeding. Award Amount: \$94,664

► Title: Oral Findings in HIV Infection: Different Risk Groups NIDR

PI: Ira Barry Lamster, D.D.S., Columbia University, New York, NY

Key Words: gender differences, HIV, oral manifestations

The goals of the project are to: (1) evaluate the occurrence, location, and severity of oral lesions in individuals in various stages of human immunodeficiency virus (HIV) infection and who are experiencing different degrees of immunosuppression; and (2) examine the progression of periodontal disease in the presence of developing immunosuppression as well as specific host responses and the nature of the periodontal microflora. The project will be expanded to increase the number of HIV-seropositive women in the study and to compare the prevalence of oral lesions in seropositive women (who acquired the virus via parenteral drug use or sexual contact with infected partners) to the prevalence seen in different groups of seropositive men (parenteral drug users and homosexual men). Award Amount: \$97,763

► Title: Drugs/AIDS Intervention Among Migrant Workers NIDA

PI: Norman Weatherby, Ph.D., University of Miami, Miami, FL Key Words: crack cocaine, HIV risk factors, Hispanic, migrant workers

The goal of the project is to prevent the spread of human immunodeficiency virus (HIV) infection among injection drug users, their sexual partners, those at demonstrable risk for initiating injection behavior, and those at risk of unprotected risky sexual behaviors resulting from their use of crack cocaine. The nature and extent of drug use and HIV-related risk-taking behaviors will be evaluated in drug-using male and female migrant workers. Approximately 100 additional Hispanic women who do not use drugs but who are sexual partners of drug users will be recruited for inclusion in the primary study. Free tuberculosis testing will be offered as a recruitment strategy. Award Amount: \$50,000

Title: Behavioral Management and Stress Responses in HIV-1 NIMH

PI: Neil Schneiderman, Ph.D., University of Miami, Miami, FL Key Words: behavioral management, HIV, stress, African American

Preliminary results have shown that participation of men in a cognitive behavioral stress management (CBSM) program produced significant decreases in depression, anxiety, and distress. The study will extend a CBSM program developed for a multiethnic sample of men with HIV infection for use among African-American women with HIV infection. Award Amount: FY 94 \$49,941; FY 95 \$49,941

► Title: The Epidemiology of HIV and Health Services Among IDUs NIDA

PI: Dale D. Chitwood, Ph.D., University of Miami School of

Medicine, Miami, FL

Key Words: barriers to health care, gender differences, injection drug use, minority

The objective of the project is to study morbidity, health care utilization, and barriers to health care among a cohort of African-American, Hispanic, and non-Hispanic Caucasian women whose drug use and sexual behaviors have been followed prospectively for five years. Approximately 150 women and 150 men from an original cohort of 601 injecting drug users will be interviewed using a standardized questionnaire to assess morbidity, utilization, and barriers to health care. Women will be compared with men to identify gender-related differences in these variables. The study will provide vital information on the problems of health care and the accessibility, acceptability, and use of care by women. Award Amount: \$50,000

► Title: Each One Teach One—St. Louis' HIV Risk Reduction Study

PI: Linda B. Cottler, Ph.D., Washington University School of

Medicine, St. Louis, MO

Key Words: AIDS, crack cocaine, gynecological manifestations of AIDS,

recruitment, risk reduction, sexually transmitted diseases

NIDA

The project supports a current NIDA-funded AIDS risk-reduction study for out-of-treatment drug users and crack smokers. The award will support the recruitment of additional women and provide for gynecological examinations and screening for gonorrhea, trichomonas, genital lice, and cervical cancer. Rates of sexually transmitted diseases (STDs) will be estimated, and associations between STDs and gynecologic problems with age, race, education, prior history of STDs, access to medical care, sexual behaviors, drug use patterns, and selected psychiatric disorders will be explored. Award Amount \$86,070

# Neurology

► Title: Prospective Neuroepidemiology of Adult Lead Exposure NIEHS

PI: Philip J. Landrigan, M.D., M.Sc., Mount Sinai School of

Medicine, New York, NY

Key Words: bones, gender differences, lead, nervous system

The purpose of the project is to determine whether the adult nervous system is more sensitive to the effects of chronic low-level exposure to lead than previously assumed. An epidemiological study is being conducted to prospectively examine occupationally exposed lead-battery workers, predominantly men. This award will support expansion of the project to include a cohort of 100 women newly hired in the construction industry. A key objective is to determine whether women sequester lead in their bones more rapidly than do men. Award Amount: FY 94 \$50,000; FY 95 \$50,000

► Title: Mechanisms of Auditory and Vestibular Dysfunction NIDCD

PI: David A. Nelson, Ph.D., University of Minnesota,

Minneapolis, MN

Key Words: animal model, auditory dysfunction, lupus, autoimmune disease

The project investigates the presence of autoantibodies in human sera of patients with systemic lupus erythematosus (SLE) with and without inner ear dysfunction. Preliminary studies in SLE patients with inner ear dysfunction showed the expected presence of autoantibody reactivity. This award will test whether inner ear autoantibodies from SLE patients can produce inner ear dysfunction and histopathology in an animal model. The inner ear antigens will be further identified via construction of an inner ear cDNA expression library and screening with human autoantibodies. Award Amount: \$49,000

#### Obesity

► Title: Body Fat Distribution and the Metabolic Profile in Women NHLBI

PI: Ahmed H. Kissebah, M.D., Ph.D., Medical College of Wisconsin,

Milwaukee, WI

Key Words: abdominal obesity, diabetes, insulin, African American

Previous investigations involving study populations of premenopausal obese and nonobese Caucasian women have demonstrated that high abdominal body fat distribution is associated with defective glucose use and subsequently overt diabetes. Data from studies conducted on Caucasian volunteers cannot be generalized to African Americans due to the unreliability of waist-to-hip girth ratios as a predictor of intra-abdominal fat deposition (as measured by

computed tomography) in African-American women. Accurate evaluation of the effects of abdominal obesity on insulin dynamics in African-American women requires that specific protocols be performed in this population. The purpose of the project is to determine the predictive power of intra-abdominal fat on cardiovascular and diabetes risk profiles in a cohort of healthy African-American women. Data from the intra-abdominal fat assessments will be used to evaluate relationships between depot size, insulin sensitivity, pancreatic insulin production, and clearance. Study results will allow for comparisons of these data by race between similar cohorts of obese and nonobese volunteers. Award Amount: \$100,000

Title: Insulin and CNS Control of Body Weight and Food Intake
 PI: Stephen C. Woods, Ph.D., University of Washington, Seattle, WA
 Key Words: animal model, body weight, central nervous system, insulin, metabolism

Evidence suggests that a definitive amount of fat is needed in order for the female reproductive system to become active. This observation is made during the transition from prepuberty to puberty or in some women athletes who decrease their body fat and become amenorrheic. The study will test the hypothesis that insulin provides an important signal that informs the brain of the current amount of fat (adiposity) in the body. An animal model will be used to evaluate the mechanism by which insulin may influence weight changes by measuring plasma and cerebral spinal fluid (CSF) insulin levels. Additional studies will be conducted to examine the interaction of insulin with anorexigenic agents, orexigenic agents, and dietary macronutrients. Award Amount: \$99,958

## Osteoporosis

► Title: Clinical and Epidemiology Research on Osteoporosis NIAMS

PI: Norman H. Bell, M.D., Medical University of South Carolina,

Charleston, SC

Key Words: genetics, vitamin D receptors, African American

This award will seek to apply and validate the recent report from Australia published in Nature on the relationship of allelic variations in the vitamin D receptor to markers of bone metabolism (osteocalcin) and bone mineral density, suggesting for the first time a gene for osteoporosis. The study tests the relationship of the gene variants to bone density and osteocalcin, a marker of bone formation, in a cohort of African-American and Caucasian women. This is an extension of the goals of the parent grant to investigate the genetic variants of the collagen molecule. In addition to determining the genotype and bone mineral density of the women, the study will investigate the function of the vitamin D receptor with skin biopsy samples. Award Amount: \$100,000

▶ Title: Rickets and Osteomalacia NIAMS

PI: John S. Adams, M.D., Cedars-Sinai Medical Center,

Los Angeles, CA

Key Words: bone mineral density, gender differences, genetics, menopause,

vitamin D receptors

Osteoporosis is four times more common in women than in men. Environmental factors such as calcium intake and exercise patterns over a lifetime play a major role, but the genetics of both vitamin D and estrogen and their receptors are the focus of new investigations of osteoporosis. The study will focus on the effect of IDBF on the binding of vitamin D and estrogen receptors to their respective response elements and the important cellular events they regulate. This may uncover and explain another level of control over bone mineral density operating during both growth and development and after menopause when bone loss predominates. Award Amount: \$83,608

► Title: Osteocalcin Synthesis and Catabolism NIAMS

Pl: Caren M. Grunberg, Ph.D., Yale University, New Haven, CT

Key Words: bone mineral density, osteocalcin, tamoxifen

Correlation of serum osteocalcin levels with rates of bone turnover has led to the wide use of osteocalcin measurement as a tool in diagnosis and in monitoring therapies. Earlier studies have suggested that tamoxifen may prevent postmenopausal bone loss. The ongoing National Breast Cancer Prevention Trial (BCPT) provides an opportunity to assess rigorously the effects of the antiestrogen tamoxifen on bone in healthy women. A new assay developed to measure serum osteocalcin levels will be validated by comparing results of serum levels as measured by the new assay with those from the conventional assay and correlation with bone density data. These data may also contribute to validating the effects of tamoxifen on bone in healthy women. Award Amount: \$74,315

► Title: Fractures in Older Women NIA

PI: Steven R. Cummings, M.D., University of California,

San Francisco, CA

Key Words: genetics, vitamin D receptors

One out of every six Caucasian women will suffer a hip fracture, one-third will develop a vertebral fracture, and over half will suffer some type of fracture during their lifetimes. The project will study the vitamin D receptor genotype of 200 women for whom serial bone mass measurements have been made over a 4-year period to confirm the ability of different alleles of the vitamin D receptor gene to predict bone density and fractures. An important outcome of this study will be the ability to predict through genetic testing a woman's risk of fractures, even at an early age. Women with a high-risk genotype may be the focus of interventions to maximize the development of peak bone mass in adolescence and to prevent bone loss during later adulthood. Award Amount: \$45,639

► Title: Multipurpose Arthritis and Musculoskeletal Diseases Center NIAMS

PI: Robert P. Kimberly, M.D., Hospital for Special Surgery,

New York, NY

Key Words: autoimmune disease, genetics, vasculitis

The project will investigate the hypothesis that in patients with vasculitis the immune complexes with IgG bind  $Fc\beta$  receptors as the first step or trigger leading to tissue damage, and that two specific  $Fc\beta$  genotypes underlie the genetic predisposition for vasculitis. The genotype for  $Fc\beta$  alleles will be determined in a broad population of patients with cutaneous necrotizing vasculitis and the IgG subclass distribution of IgG contained within immune complexes will be characterized. These data will determine whether there is a basis for studying the relationship of  $Fc\beta$  alleles as an important genetic marker or risk factor in a variety of autoimmune diseases prevalent in women. Award Amount: \$50,000

► Title: Calcium on Bone Mass Formation During Puberty NIAMS

PI: Velimir Matkovich, M.D., Ph.D., Ohio State University,

Columbus, OH

Key Words: bone mineral density, calcium intake, genetics, vitamin D

receptors, adolescents

A recent article in Nature described a relationship between allelic variations in the vitamin D receptor and bone mineral density. This suggests for the first time a gene for osteoporosis. A substantial amount of data has been accumulated on the skeletal status and calcium intakes of a cohort of adolescent females, including information on their families. An ongoing clinical trial designed to test the effect of calcium supplements (1,000 mg/day) on adolescent bone development will be expanded to correlate bone mineral density with the genotype for the

vitamin D receptor in this sample population. These data will provide an important validation of the association between genetic influence and bone mineral density. Award Amount: \$100,000

► Title: Effects of Lactation and Weaning on Calcium Status NIAMS

PI: Bonny L. Specker, Ph.D., Children's Hospital Research

Foundation, Cincinnati, OH

Key Words: bone mineral density, calcium intake, lactation, vitamin D receptors

The objective of the project is to determine whether there are significant changes in bone mineral content and calcium homeostasis during lactation and during the postweaning period, and whether any changes during those periods can be affected by calcium intake. The project will be expanded to include genotyping for the vitamin D receptor alleles. The study will determine if the losses during lactation or the gain during weaning are associated with a particular genotype. Award Amount: \$81,572

► Title: Risk Factors for Vertebral Fracture and Bone Loss NIAMS

PI: Douglas P. Kiel, M.D., Hebrew Rehabilitation Center for Aging,

Boston, MA

Key Words: bone density, gender differences, genetics, vitamin D receptors

The project examines the risk factors for osteoporosis and fractures in the Framingham cohort. This population-based cohort of women and men has been studied longitudinally for more than 25 years for a variety of disease outcomes but primarily for cardiovascular disease. Data previously collected on the bone density and vertebral fracture incidence of 300 females will be combined with the analysis of the vitamin D receptor genotype to test, in a population-based cohort, the correlation of the vitamin D receptor alleles with bone density phenotype. Award Amount: \$50,000

► Title: Estrogens and Osteoclastogenesis NIAMS

PI: Starvos C. Manolagas, M.D., Ph.D., University of Arkansas for

Medical Sciences, Little Rock, AR

Key Words: estrogen, menopause, osteoblast formation, African American

The project tests the hypothesis that loss of estrogen leads to increased production of cytokines and, in turn, to increased osteoclast (bone-resorbing cell) development. Cultures of bone marrow samples previously collected in a study of osteoclast development will be examined for changes in osteoblast (bone-forming cell) development. A previously developed osteoclast protocol will be applied to bone marrow aspirates of eight African-American and eight Caucasian premenopausal women to determine whether the well-established difference in osteoporotic fracture risk between African Americans and Caucasians is reflected in the regulation of osteoclastogenesis. If confirmed, this model could reflect an important mechanism underlying the high risk of osteoporotic fracture in postmenopausal women. Award Amount: \$100,000

## Violence

► Title: Impact of Family Violence on Women's Drug Use NIDA

PI: Brenda A. Miller, Ph.D., Research Institute on Addictions,

Buffalo, NY

Key Words: drug crimes, victimization, prison

There is little empirical data on the relationship between drug use and childhood victimization or adult experiences with partner and nonpartner violence among incarcerated women.

The study examines how adult violent victimization (both partner and nonpartner) related to the use of illicit drugs and whether drug use contributes to the risks for violent victimization of women. This award will expand the study to include a sample of women from the Bedford Correctional Facility, New York State's maximum security prison (60 percent to 65 percent convicted of drug-related crimes). Histories of victimization of incarcerated women with and without drug-related offenses will be compared. Award Amount: \$49,814

Fluoxetine Treatment of Post-Traumatic Stress Disorder
PI: Jonathan R.T. Davidson, M.D., Duke University, Raleigh, NC
Key Words: barriers to treatment, fluoxetine, post-traumatic stress disorder, rape

The project is a placebo-controlled, double-blind trial of the effects of fluoxetine (Prozac) on the treatment of post-traumatic stress disorder (PTSD) among women who have been raped. This award will expand the project to explore how psychological, social, and cultural barriers prevent rape victims with PTSD from seeking treatment and participating in research studies. Award Amount: \$49,361

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